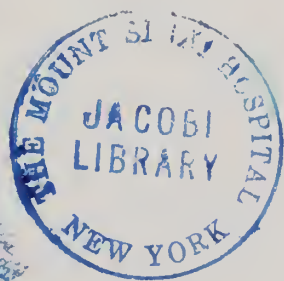




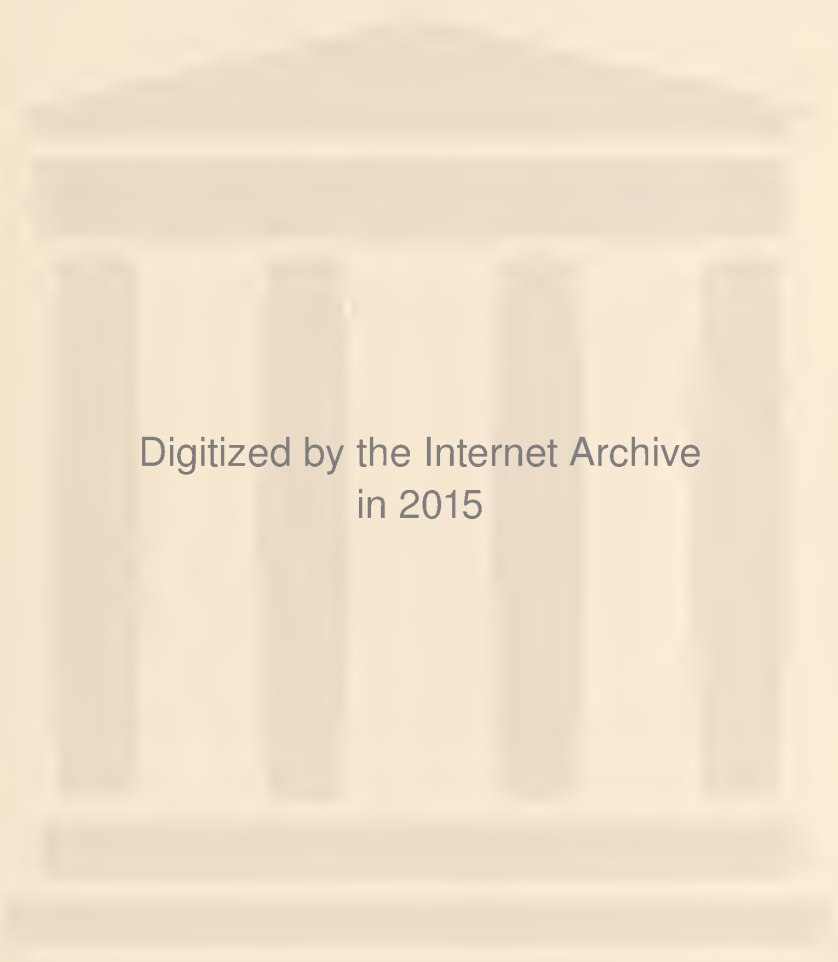


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**VOLUME XXVII**

**1961**

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## **Daniel Stats Memorial Prize**

The Dr. Daniel Stats Memorial Committee is pleased to announce its annual award. By terms of the Fund, the award is granted to a member of the House Staff who during the current academic year has published or has accepted for publication, the most meritorious paper on a subject with hematologic orientation. The Committee unanimously chose:

“The Effect of Urine Hydrolysis on  
Nucleoproteins in Normal, Leukemoid  
and Leukemic Leukocytes”

by  
Dr. Alan Solomon

Dr. Solomon received a B.S. degree from Bucknell University, and his M.D. degree from Duke University. He interned at The Mount Sinai Hospital, was an Assistant Resident for one year at Montefiore Hospital, and the following year at The Mount Sinai Hospital. At present he is a Clinical Associate at the National Cancer Institute of the National Institutes of Health. He will be a resident in medicine at The Mount Sinai Hospital in 1962. Dr. Solomon plans to practice internal medicine and continue investigative work in immunology and protein chemistry.

It is the hope of the Committee that subsequent awards will equal the quality of this year's selection.

Alexander B. Gutman, M.D.  
Alan F. Guttmacher, M.D.  
Lester R. Tuchman, M.D.  
Louis R. Wasserman, M.D.



PATTERNS OF BONE CHANGE IN THE LEUKEMIAS  
AND MYELOSCLEROSIS<sup>1</sup>

JOHN E. MOSELEY, M.D.

*New York, N. Y.*

## LEUKEMIA

Recent statistical reports indicate that the incidence of leukemia is increasing (1). It has not been satisfactorily established, however, whether these findings represent a real increase in the occurrence of this disease or, in fact, reflect only the increased and improved diagnostic facilities now available. At any rate, greater numbers of cases of leukemia are being seen now than in previous periods and there is no doubt that leukemia is currently one of our major health problems.

The clinical course of this disease may be acute or chronic. In acute cases the period of survival is a year or less from the time of onset of symptoms. The survival times in chronic leukemia are subject to marked variations but the average duration is about three years.

Leukemia affects individuals of all ages. In children it almost always runs an acute course. Opitz (2) found that 95.8 per cent of a series of 1357 cases in children were of the acute form. Cooke (3) found that 95 per cent of 294 cases of childhood leukemia were acute. Both acute and chronic forms of the disease occur in adults. The acute form is seen more frequently among younger adults while the chronic leukemias have their greatest incidence in the older age groups. The maximum incidence of chronic granulocytic leukemia is observed between the ages of 35 and 45 years. The maximum incidence of chronic lymphatic leukemia is considered to be in the decade between 45 and 54. Rosenthal and Harris (4), however, obtained a maximum incidence for this type of leukemia between the ages of 50 and 69 years. In any case, chronic lymphatic leukemia in practically all studies is shown to occur at definitely older ages than any other form of the disease.

Radiographically demonstrable bone changes occur much more commonly in children than in adults. Baty and Vogt (5) found bone changes in 70 per cent of 43 cases of childhood leukemia. Silverman (6) reporting on a series of 103 cases in children found bone changes in 51 per cent of them. More recently Willson (7) analyzed 140 cases in children ranging in age from less than 6 months up to 13 years and found the incidence of roentgenologically demonstrable skeletal lesions to be 64 per cent. The incidence of skeletal changes in adults is less certain but the usually quoted figures are 8 to 10 per cent.

<sup>1</sup> From the Department of Radiology, The Mount Sinai Hospital, New York 29, N.Y.

It is generally considered that bone changes are more frequently demonstrated in children because the marrow spaces in childhood are occupied mostly by hematopoietic tissue, leaving little space for expansion of the proliferating leukemic cells which eventually encroach upon the bone itself. In adults very little hematopoietic tissue remains in the peripheral skeleton and there is much greater reserve space in the fatty marrow cavities. Other factors which contribute to the osseous changes in leukemia are a general interference with nutrition and stimulation of osteolytic and osteoblastic activity by the leukemic cells.

#### BONE LESIONS IN CHILDREN

The occurrence of bone lesions in acute leukemia in children generally increases with the duration of the disease but changes may occur with surprising rapidity in some cases and may be seen as early as a month after the onset of symptoms. On occasion lesions may not appear until quite late and in some instances no skeletal abnormalities are demonstrated at any time during the course of the illness. As is the case in so many instances of disease reflected in abnormalities of the growing skeleton, the bone changes in childhood leukemia are most often found in the areas of most rapid growth. Thus the knees, wrists and ankles are usually the sites of the earliest changes. When bone changes are present the knees are almost invariably affected, and when bones are studied with the possibility of leukemia in mind, the knees and wrists should be considered the optimal sites for examination. Changes at the shoulders, hips and elbows are relatively infrequent unless the disease is well advanced.

The bony defects have been divided into four types: 1) a transverse line or band of diminished density at the ends of the long bones; 2) osteolytic lesions; 3) periosteal elevation and new bone formation; 4) osteosclerosis. A transverse radiolucent line or band across the metaphysis adjacent to the epiphyseal plate is the earliest and most frequent type of involvement. It may occur as the only demonstrable bone change or it may be found in association with other forms of bone involvement. Willson (7) found this type of bone lesion in 86 per cent of 89 cases which had some form of leukemic bone defect. In 36 per cent of the cases it was the only bone change present while in 50 per cent it was found in association with other osseous leukemic lesions.

The metaphyseal transverse radiolucent area varies in width. It tends to extend across the metaphysis from one cortex to the other (Fig. 1). In early cases, however, the line may be incomplete. In some instances it may be as thin as a pencil line and measure no more than 1 mm. The early description of this zone in 1935 by Baty and Vogt (5) characterized it as a narrow transverse zone of diminished density measuring from 2 to 5 mm in width. On occasion the lucent line will be sandwiched between the dense zone of provisional calcification and a growth line or band of increased density on its shaft side (Figs. 2, 3). In other cases the lucent band will gradually fade into the adjacent spongiosa (Fig. 4). The zone of provisional calcification is usually sharply etched, homogeneous and unbroken as is the metaphyseal cortex which surrounds the lucent area. This

metaphyseal line is one of the early changes in leukemia and is frequently present when the skeleton is otherwise unaffected. In advanced cases it may be associated with erosion of the cortex but in such instances there is usually evidence of osteolysis as well.

The pathological basis for the metaphyseal transverse zones of radiolucency is considered to be a depression of endochondral bone formation related to the child's general illness. To this is added the atrophy due to pressure of the pro-

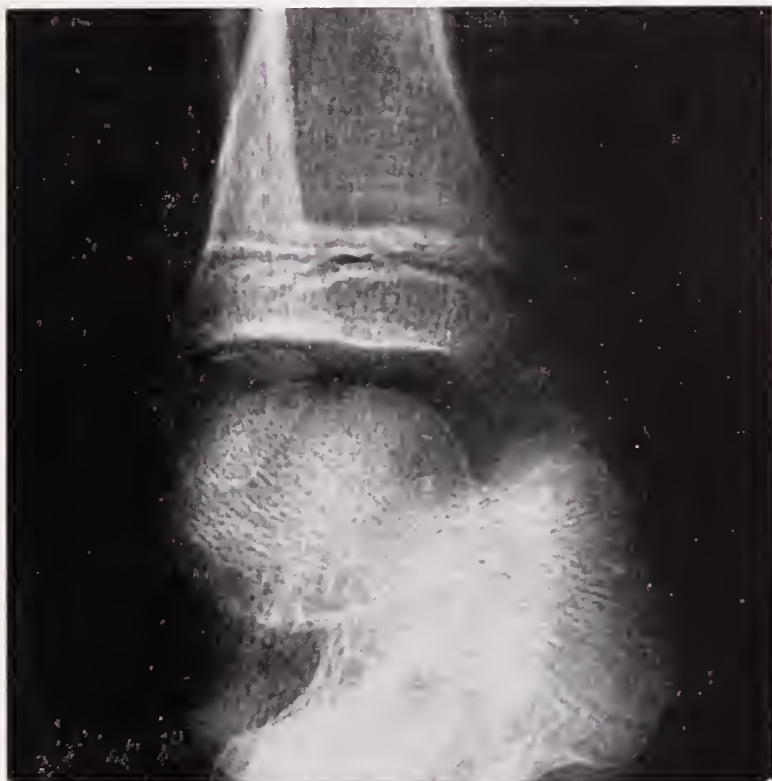


FIG. 1. Three year old child with acute lymphatic leukemia. There is a very thin transverse lucent line which extends across the distal metaphysis of the tibia above the epiphyseal plate. The plate is intact and there is no erosion of the metaphyseal cortex.

liferating leukemic cells on the osseous trabeculae. As leukemic cells continue to proliferate and infiltrate the bone marrow a wide zone of decalcification occurs in the metaphysis often involving the whole of this part of the bone and incorporating the zone of radiolucency so that it is no longer visible as a discrete line or band.

The metaphyseal transverse zone of radiolucency is not pathognomonic for leukemia. It is a nonspecific process which may be seen in infants and children who suffer other severe illnesses. In these instances it is apparently the result of a disturbance in endochondral bone growth alone. Somewhat similar zones occur

in scurvy due to trabecular atrophy (scurvy lines) and in syphilis due to replacement of bone by syphilitic granulation tissue (metaphysitis). Willson (7) reviewed 740 consecutive long bone examinations in children and found that 32 of them, other than those with leukemia, showed a metaphyseal radiolucent line. Twenty-eight of the patients showing such a line were under the age of two. Only four patients 2 years old or older exhibited such a line. None of these four cases resembled leukemia clinically. Of the 28 cases under the age of two, five were cases of infection (septicemia, staphylococcal arthritis and meningitis) which



FIG. 2. Leukemia. A transverse line of radiolucency is sandwiched between the intact zone of provisional calcification and a growth line. The diminished density of the metaphyseal transverse line is best appreciated at the tibial and fibular metaphyses.

did resemble leukemia clinically early in their course. Figure 5 shows a wide metaphyseal band of radiolucency in a 6 day old infant suffering from an acute septicemia. This band disappeared after the infection was controlled.

The vast majority of cases of childhood leukemia occur during the first five years of life. The peak incidence is between two and five. Only about 10 per cent of cases occur under the age of two. Since 90 per cent of cases occur after the second year when the metaphyseal line is not often seen in other conditions, the occurrence of this finding in children over two takes on added importance, and, in fact, some degree of specificity.

The appearance of osseous metastases in neuroblastoma mimics quite closely,



the bone changes in leukemia. Advanced bone changes in leukemia are, in fact, impossible to distinguish from those of neuroblastoma. A typical narrow transverse line of radiolucency must be rare in neuroblastoma. We have not seen it. Willson reviewed 30 cases of proved neuroblastoma and was unable to find any showing a radiolucent line at the metaphysis. Sherman and Leaming (8) studied 37 cases of neuroblastoma with bone metastases and were unable to find any



FIG. 3. Ankle of 3 year old child with acute lymphatic leukemia. There is a sandwich type metaphyseal line of radiolucency at the distal end of the tibia. At the distal fibular metaphysis there is a lucent line without a proximal band or line of sclerosis.

transverse bands of decreased density at the metaphyses and Kincaid, Hodgson and Dockerty (9) reporting on 14 cases of metastatic neuroblastoma were similarly unable to find this type of metaphyseal lesion.

The concept of a metaphyseal transverse line of radiolucency, however, has been subjected to various interpretations. As noted above, in any severe illness disturbances in endochondral bone formation, most apparent at the sites of most rapid growth, occur frequently. While in some instances, particularly in the very young, this may be reflected in a line of diminished density indistinguish-

able from the metaphyseal line described in leukemia, more often the disturbance in bone formation is represented by a growth line of increased density which extends across the metaphysis, completely or incompletely, at varying distances from the zone of provisional calcification. This is apt to create a sandwich-like effect but the bone between the calcified cartilage and the growth line has a density similar to that of the adjacent spongiosa. Sometimes multiple growth lines occur in response to remissions or to variations in severity of the disease process (Fig. 6). Trophic disturbance such as this may be seen in neuroblastoma and may mimic the metaphyseal line of radiolucency. Furthermore,



FIG. 4. Leukemia. Metaphyseal transverse lucent areas in tibia and fibula. The bands fade into adjacent spongiosa. The zones of provisional calcification and the metaphyseal cortices are intact.

in some cases there may be a wide area of decalcification at the metaphysis due to destruction by the metastatic tumor. In practically all cases of neuroblastoma where there have been changes at the metaphysis with any similarity to the metaphyseal line of radiolucency there have been more extensive associated changes in the metaphysis or further up the shaft (Fig. 7). One does not find an otherwise unaffected long bone with a metaphyseal line as described in leukemia. Moreover, as in metastatic malignancies in general, metastatic neuroblastoma only occasionally metastasizes to bones distal to the knees and elbows. Where there is widespread involvement by leukemia, on the other hand, osseous changes are not unusual in the most distal portions of the extremities (Fig. 8).

Pathologic study of the transverse band of diminished density in leukemia

suggests that this lesion is the result of interference with nutrition and of destruction by proliferating leukemic cells. Silverman (6) has cited two cases observed by him in which transverse bands in leukemia disappeared. In one case the bands disappeared during a remission when the child's nutrition improved. In the other case the bands faded while the child was under penicillin therapy for a secondary infection. The use of antimetabolites and ACTH may induce remissions in an appreciable number of children and such children sometimes show definite regression of the bony lesions, particularly the metaphyseal band. The bands increase in density and are sometimes denser than the adjacent uninvolved bone (Fig. 9). As a matter of fact, resolution of these bony lesions may occur

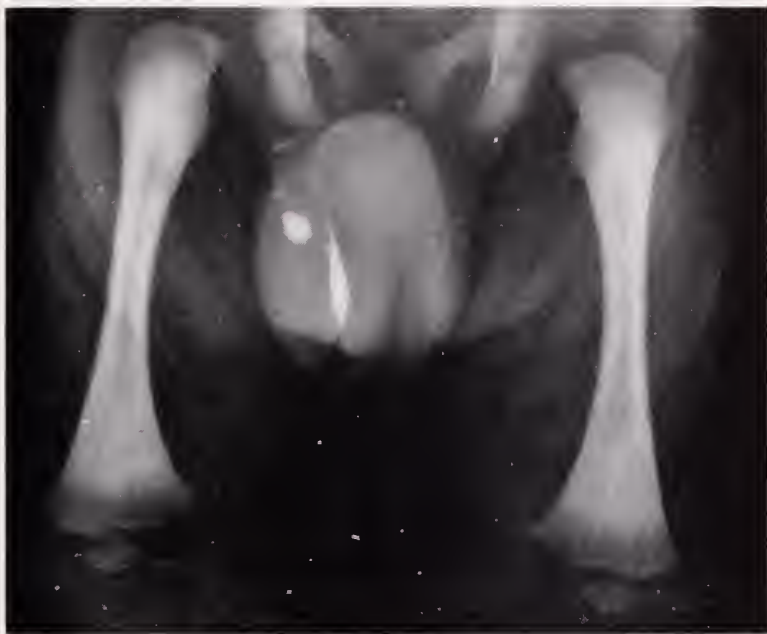


FIG. 5. There is a wide metaphyseal band of lucency in a 6 day old infant suffering from an acute septicemia.

following local irradiation (10) and after the mere immobilization of the affected part (11).

Osteolytic lesions are next in frequency to the metaphyseal bands. In Willson's series they occurred in 59 per cent of the cases showing bone involvement. The lytic lesions may be localized or diffuse and generally appear first in the spongiosa of the long bones, later developing further down the shaft. Although they are more frequent in the long bones they may be found in any portion of the skeleton. This type of involvement may be represented by small, more or less punctate lesions (Fig. 10), by larger single or multiple areas of destruction (Fig. 11) or by a diffuse demineralization and sometimes a washing-away of bony architecture, frequently at the metaphysis, with or without extension into the shaft (Figs. 12, 13).

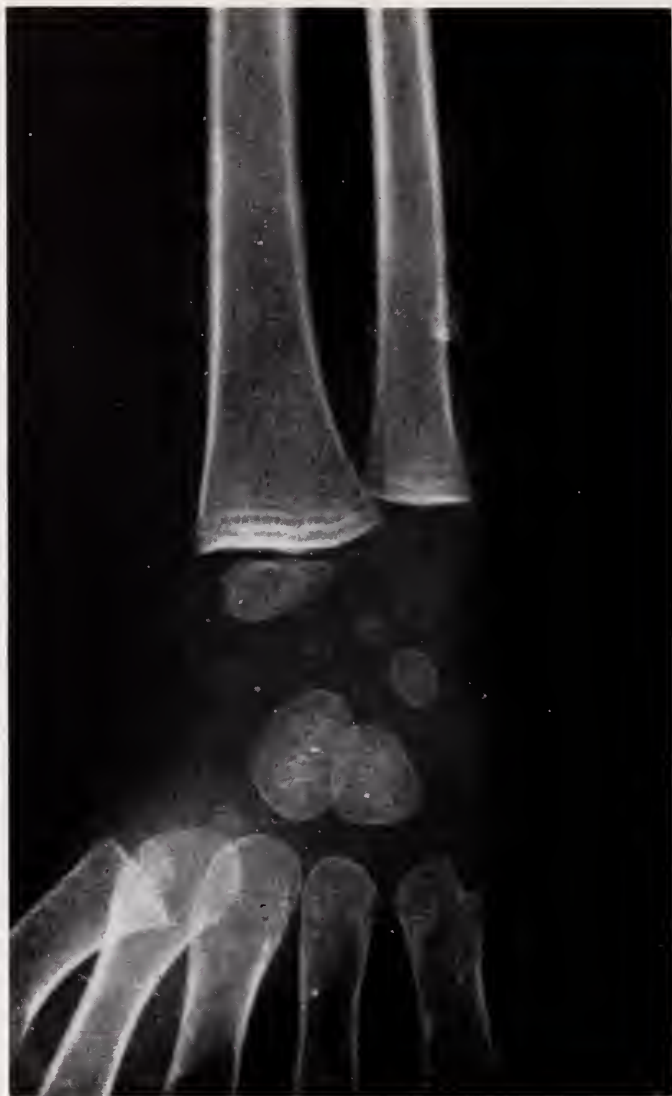


FIG. 6. Four year old child with acute osteomyelitis of humerus. There are multiple growth lines at the distal ends of the radius and ulna. Note that the spongiosa between these lines is not diminished in density. Such lines may appear in any severe illness and represent disturbance in endochondral bone formation. They are most frequently seen at the sites of most rapid bone growth.

Periosteal reaction may occasionally occur as the only manifestation but usually it is found in association with other changes (Fig. 14). Willson found periosteal lesions in 33 per cent and Silverman in 32 per cent of cases with skeletal changes. While periosteal lesions are seen most frequently in the long bones they may be found in the short tubular bones and ribs as well. The periosteal



FIG. 7. Knee of a 4 year old child with neuroblastoma. There are transverse bands at the femoral and tibial metaphyses. At the tibial metaphysis this band is associated with mixed productive and destructive changes. At both metaphyses the density of the bone between the parallel lines is not diminished. The appearance is created by growth lines which parallel the zones of provisional calcification.



reaction results from stimulation of the periosteal osteoblasts by leukemic cells interspersed between the cortex and periosteum.

Osteosclerotic lesions rarely occur as the only osseous manifestation of leu-



FIG. 8. Foot of 1½ year old child with acute lymphatic leukemia shows lucent band lesions at the metaphyses of the metatarsals. There has been erosion of the adjacent cortex at the distal ends of some bones. There are typical transverse radiolucent bands at bases of the proximal phalanges of the first and second toes. Small focal areas of osteolysis are noted in the metatarsal shafts.

kemia but may be found together with osteolytic lesions resulting in mixed productive and destructive mottled patterns (Fig. 15).

It is interesting to note that leukemic cells may infiltrate the margins of the cranial sutures in children resulting in the appearance of diastasis. The fact that metastatic neuroblastoma may involve the skull and brain with resultant separation of the sutures is frequently used as a factor in differentiating between neuroblastoma and leukemia when the long bone changes do not permit the differentiation. Hitzig and Siebenmann (12) have reported two cases presenting the

appearance of suture separation due to leukemic infiltration of the suture margins. This manifestation is rare in leukemia, however, and the occurrence of suture separation in the presence of bone changes consistent with leukemia or



Fig. 9. This is the patient shown in Fig. 1 after a course of treatment with antimetabolites. The transverse band is now greater in density than the adjacent bone.

neuroblastoma, must be considered evidence strongly favoring the latter condition (Figs. 16, 17).

The clinical diagnosis of leukemia in infants and children is often difficult because the clinical manifestations are usually nonspecific and suggestive of more common conditions such as rheumatic fever and rheumatoid arthritis. The difficulty is compounded by the often confusing blood picture. In a large proportion of these patients the number of white blood cells in the circulation is nor-



FIG. 10. Leukemia. There are small areas of osteolysis in the shaft of the tibia. These vary in size and some of them are longitudinal in axis. There is a more diffuse lucency at the metaphysis. Slight periosteal reaction is demonstrated along the posterior tibial cortex.



FIG. 11. Leukemia. There are large areas of osteolysis involving the metaphyses of the radius and ulna. The bones are generally demineralized with a coarse trabecular pattern and there is slight periosteal reaction along the shaft of the ulna.



mal or reduced. In such instances the radiographic demonstration of bone changes suggesting leukemic involvement can be of considerable importance to the clinician and, on occasion, may be the leading factor in arriving at the correct diagnosis.

#### BONE LESIONS IN ADULTS

Bone changes are far less common in adults suffering from leukemia than they are in children with this disease. The generally quoted incidence of 8 to 10 per



FIG. 12. Boy with acute myelogenous leukemia. There are multiple large and medium-sized areas of osteolysis involving the metaphyses of the radius and ulna. There has been cortical destruction on both sides of the ulnar metaphysis and on the medial aspect of the radial metaphysis.

cent for bone changes in adults is in marked contrast to the 60 to 70 per cent incidence in infants and children. Jaffe (13), in fact, challenges the incidence of 8 to 10 per cent for adults and suggests that it includes many cases of lymphosarcoma in which the terminal blood picture presents as a lymphocytic leukemia.

It is indeed rare to find any skeletal manifestations in the acute leukemias of the adult. One is occasionally surprised, however, by finding extensive osseous involvement in an acute case. The vast majority of adults showing bone changes suffer from the chronic form of the disease. Of these the greater number are victims of chronic lymphatic leukemia. Demonstrable bone involvement in myelogenous leukemia is seen infrequently. The rare chloroma, however, is an exception to the rule. These greenish tumor masses represent localized collections

of leukemic cells and are almost always expressions of a myelogenous leukemia. They are highly invasive and destructive growths which commonly involve bone. The skull, facial bones and sternum are frequently affected. The ribs, spine and pelvis are also often involved but the long bones are less commonly the sites of chloroma formation.

The metaphyseal line of radiolucency is rarely seen in the adult. There is more apt to be a generalized demineralization of the bones. This is due to osseous resorption resulting from expansion of leukemic tissue. In the adult, active marrow is concentrated in the more central segments of the skeleton. Thus, changes are



Fig. 13. Leukemia. There is diffuse decalcification at the ends of the tibia and fibula. Numerous small areas of osteolysis extend from the metaphyses into the shafts. Slight periosteal reaction is noted along the medial aspects of both bones. The lateral cortex at the distal end of the tibia has been eroded.

more pronounced in the spine, ribs, skull and pelvis. The spine, particularly, may be the site of marked demineralization with severe cupping or collapse of one or more vertebrae (Fig. 18).

As in childhood leukemia there may be scattered, more localized areas of rarefaction. These may be of various sizes and may involve almost any portion of the skeleton including the small tubular bones of the hands and feet. In this latter regard, such leukemic lesions differ from the usual neoplastic metastases which tend not to involve bones distal to the elbows and knees. The areas of osteolysis are the sites of localized bone destruction by proliferating leukemic cells (Fig. 19).

When leukemic tissue extends beneath the periosteum there may be reactive

periosteal new bone deposition. Sometimes the perforating leukemic cells erode all or a part of the cortex (Fig. 20).



FIG. 14. Two year old female with acute lymphatic leukemia. The changes at the knee are advanced. There are large areas of osteolysis at the metaphyses of the tibia and femur. The adjacent cortices have been eroded and there is marked periosteal reaction with early new bone formation. The zones of provisional calcification are destroyed in their central portions.

Diffuse osteosclerosis is seldom seen in true leukemia in the adult. Fibrosis of the bone marrow may occur in long standing cases of leukemia and, on rare occasions, osteosclerosis may develop. But many cases so categorized are more likely to be instances of myelosclerosis with a terminal leukemoid blood picture.

## MYELOSCLEROSIS

Myelosclerosis is a term used to designate a hematologic disorder characterized by fibrotic or sclerotic changes in the bone marrow, anemia and marked splenomegaly due to myeloid metaplasia. This condition has been described under



FIG. 15. Leukemia. The tibial shaft is involved by osteolytic and osteosclerotic changes. There are anterior and posterior perforations of the proximal tibial cortex.

a variety of names including "agnogenic myeloid metaplasia," "megakaryocytic myelosis," "myeloid metaplasia," "myeloproliferative syndrome," "leukanemia," "osteosclerotic anemia," "myelofibrosis" and many others. While there may be significant variations in the clinical and laboratory findings in myelosclerosis, the typical picture is that of an insidious onset of weakness, fatigue, dyspnea and weight loss. There is usually pallor and hepatosplenomegaly. The spleen frequently reaches marked degrees of enlargement. Most often there is progressive

anemia. The peripheral blood contains numerous immature red cells and immature leucocytes. The marrow usually either cannot be aspirated or yields only a few marrow cells and some blood. In advanced cases the hematopoietic elements of the marrow will have been replaced by fibrous or osseous tissue or both. This is usually determined by bone biopsy rather than aspiration. The condition is essentially a disease of middle or late life. In a series of 25 cases studied by Leigh *et al.* (14), the age at the time of diagnosis ranged from 34 to 85 years.

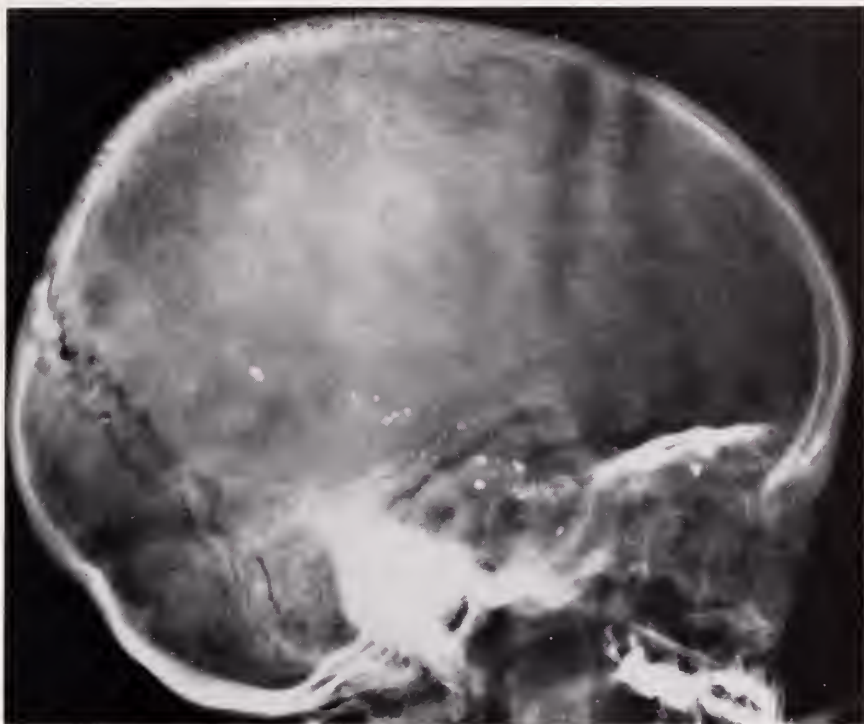


FIG. 16. Four year old child with neuroblastoma. There is separation of the sutures, particularly the coronal. Numerous small areas of destruction are seen in the bones of the vault and there is some radial striation of thickened diploic trabeculae in the parietal region. These findings are characteristic of metastatic neuroblastoma.

Eighty-four per cent of the cases were 50 years of age or older. Jacobson and his associates (15) reviewed twenty cases and found the age range to be from 41 to 72 years. Half of the patients were in their sixth decade when first seen. The sex distribution is more or less even, varying slightly with different series.

In its fully developed form myelosclerosis may be considered a fairly distinct entity but in many cases it may be difficult to differentiate from myelogenous leukemia. Some hematologists, in fact, consider the two conditions to be variations of the same disorder. Myelosclerosis may develop after long standing polycythemia, but in many instances there is no evidence of any preceding blood disease. Wasserman (16) studied 61 cases of myeloid metaplasia with myelofi-



brotic marrows and found that 58 per cent of them had a probable antecedent polycythemic phase while 42 per cent were apparently idiopathic. In the terminal stages of the condition it is not uncommon for the patient to develop a blood picture similar to that of myelogenous leukemia. The relationship between myelosclerosis and the myeloproliferative disorders is still a perplexing area of speculation and research.

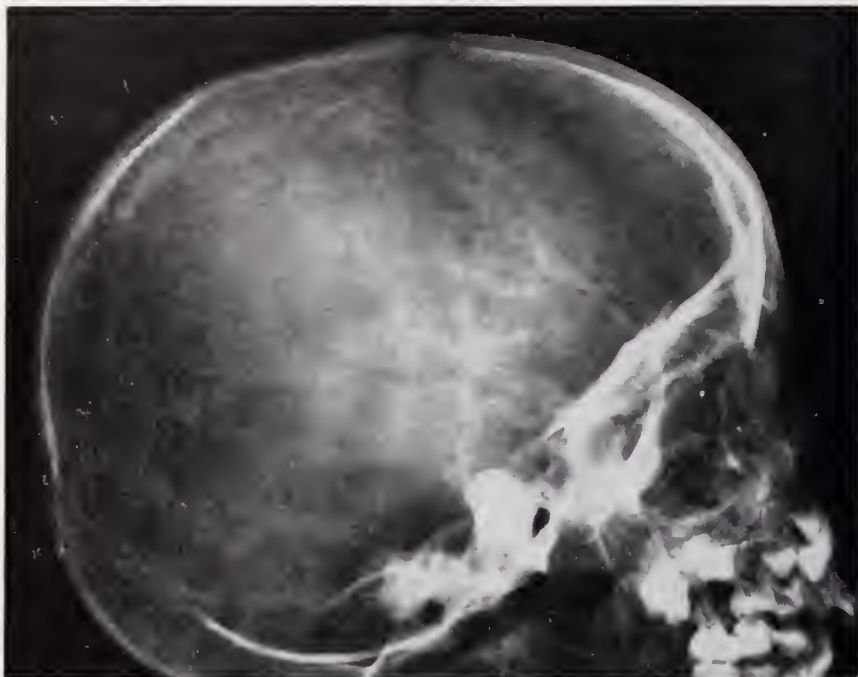


FIG. 17. Skull of child with acute lymphatic leukemia. There are numerous scattered small areas of lysis in the bones of the vault. No suture separation nor radial striation of diploic trabeculae can be demonstrated.

#### BONE LESIONS IN MYELOSCLEROSIS

The reported incidence of radiographically demonstrable bone lesions in myelosclerosis varies. Sussman (17) considered that about one third of all cases of myelosclerosis show bone changes that are detectable roentgenographically. Leigh *et al.* (14) reporting on a series of 25 cases found slightly more than half of them to show osteosclerosis. Jacobson *et al.* (15) found demonstrable bone changes in all of the twenty cases reported by them. Variation in the reported incidence of bone changes is apparently due to difficulty in evaluating mild changes in the density of bones. Individual differences in bone structure and variations in radiographic technic make minimal increases in bone density difficult to appraise.

In the later stages of a certain number of cases of myelosclerosis there is new bone formation. New bone is laid down on the surfaces of the old osseous trabeculae. This leads to the appearance of thickening of the trabeculae, notably in the



FIG. 18. Adult patient with chronic lymphatic leukemia. The spine shows marked demineralization. There is compression of several of the weakened vertebrae with widening of the intervertebral spaces and some associated productive change.

cancellous bone. Eventually new bone trabeculae are formed in the marrow spaces by precipitation of calcium in the reticular matrix (18). The radiographic appearance of well delineated bone trabeculae is replaced by what Sussman (19) refers to as an overall ground glass appearance (Fig. 21). Increase in density of



FIG. 19. Same patient as Fig. 18. There are irregular areas of osteolysis scattered throughout the medullary cavity of the femur. Most of these have their long axis parallel to the long axis of the bone.

the bones may be uniform or may be associated with patchy areas of bone condensation. Frequently small, rounded areas of radiolucency are scattered through the dense bone representing areas of myelofibrosis (Figs. 22, 23). In some cases this may be the predominant finding (Fig. 24).

A feature which is frequently present, but which has received no comment in the literature is coarse periosteal new bone formation characteristically localized along the medial margins of the distal femoral shafts and the lateral margins



of the upper tibial shafts (Fig. 25). A similar form of periosteal reaction is often demonstrated at the ankles (Fig. 26). There may be areas of periosteal reaction in other portions of the long bones but involvement of the sites described above at the knees and ankles occurs with enough frequency to warrant consideration



FIG. 20. Patient with chronic lymphatic leukemia. There are multiple areas of osteolysis involving the proximal humerus. A large area of destruction is seen in the region of the tuberosity. There is partial erosion of the upper medial humeral cortex. Irregular areas of destruction are present in the scapula as well.

of such features among the characteristic osseous changes in myelosclerosis. Another roentgen feature which, although commonly seen, has received little attention in previous descriptions, is thickening of the inner aspects of the cortices of the long bones with resultant narrowing of the medullary spaces (Fig. 27). This is the result of newly formed bone having been laid down on the inner surface of the cortex (18) and is identical to the changes seen in long bones in the later stages of sickle cell disease.

The roentgen changes are more frequently seen in the central skeletal segments. Thus, the thoracic cage, pelvis, dorsal and lumbar spine and proximal portions of the humeri and femora are most often involved. Involvement of the



FIG. 21. Myelosclerosis. The tibia shows a ground glass appearance due to formation of new bone trabeculae and thickening of old trabeculae. The medullary area is being filled in by new trabecular bone.

more peripheral segments of the long bones, however, is by no means unusual. Even the hands and feet, on rare occasions, may be involved.

The concept that there is no involvement of the skull in myelosclerosis appears, somehow, to have taken root in much of the literature on this disorder. It is true that changes in the skull, when they occur, may be difficult to evaluate.

This presumably has led to the erroneous impression that the cranial bones are not involved in this condition. Skull changes do occur in some cases and may be of three types. In some instances there is a generalized increase in the density of



FIG. 22. Myelosclerosis. There are patchy areas of bone condensation, thickened trabeculae and scattered areas of radiolucency in the humerus, scapula and acromion.

the bones. The diploic space is obliterated and the vascular markings diminished. Those that remain are prominent against the background of diffusely sclerotic bone (Fig. 28). Such changes may vary from minimal to advanced and may be difficult to evaluate in the minimal to moderate cases. A less common form of involvement is that in which small rounded lucent areas are scattered through the bones of the calvarium. There is no associated appreciable increase in the

overall density of the skull (Fig. 29). A third type combines the small scattered osteolytic areas with a generalized increase in the calvarial density. Although skull changes have been considered rare or non-existent in this disease, Jacobson *et al.* (15) found the skull to be involved in 5 of 20 cases. Even when the skeletal changes are outstanding, however, the skull findings are seldom dramatic. They practically never, for instance, reach a stage of development comparable to advanced forms of Paget's disease.



FIG. 23. Myelosclerosis. There is an overall increase in the density of the bones of the pelvis and femora. This is due to trabecular thickening and patchy areas of bone condensation. In the ischia there is an increase in the fine trabecular structure resulting in an almost homogeneous increase of density. Numerous small areas of lucency representing foci of fibrosis are seen scattered throughout the bones.

When there is involvement of the thoracic cage especially in association with elevation of the left diaphragm by an enlarged spleen, the diagnosis can be suggested from a simple chest film. The presence of a very large spleen is important in the differential diagnosis of myelosclerosis but it should not be forgotten that splenomegaly is not present in *all* cases and that when present it does not *always* attain the huge dimensions which are characteristic of myelosclerosis. Of the twenty cases studied by Jacobson (15) one showed a normal sized spleen and in two the spleen was only slightly enlarged.

In considering the differential diagnosis of myelosclerosis one should keep



firmly in mind the fact that this condition is essentially a disorder of middle and late life, that it is usually accompanied by a fairly characteristic blood picture including the presence of many immature red and white blood cells and that



Fig. 24. Myelosclerosis. There is extensive involvement of the ribs, spine and pelvis by diffuse trabecular thickening and multiple small areas of lucency. Practically the entire skeleton including the skull was involved. The patient was a 68 year old woman in whom myelosclerosis was preceded by polycythemia vera. In addition to osseous involvement the shadow of a large spleen can be seen in the left abdomen extending below the crest of the left ilium. The liver is also enlarged.

there is most often a very large spleen and other evidence of extramedullary hematopoiesis. The bone changes are usually diffuse and symmetrical but cases may be encountered where trabecular thickening, small lucent areas of fibrosis or both are localized to one or two portions of the skeleton and the remaining bones show no abnormality.

In osteopetrosis or marble bone disease there is a symmetrical increase in the density of the bones with loss of the normal trabecular pattern. In some instances this disease begins in utero, follows a malignant course with extreme bone changes and death occurs in infancy. In other cases the condition is less fulminating and the patients survive infancy but eventually succumb in childhood. There is another smaller group of cases, however, in which the patients appear clinically normal in childhood and adolescence but in whom the disease is dis-

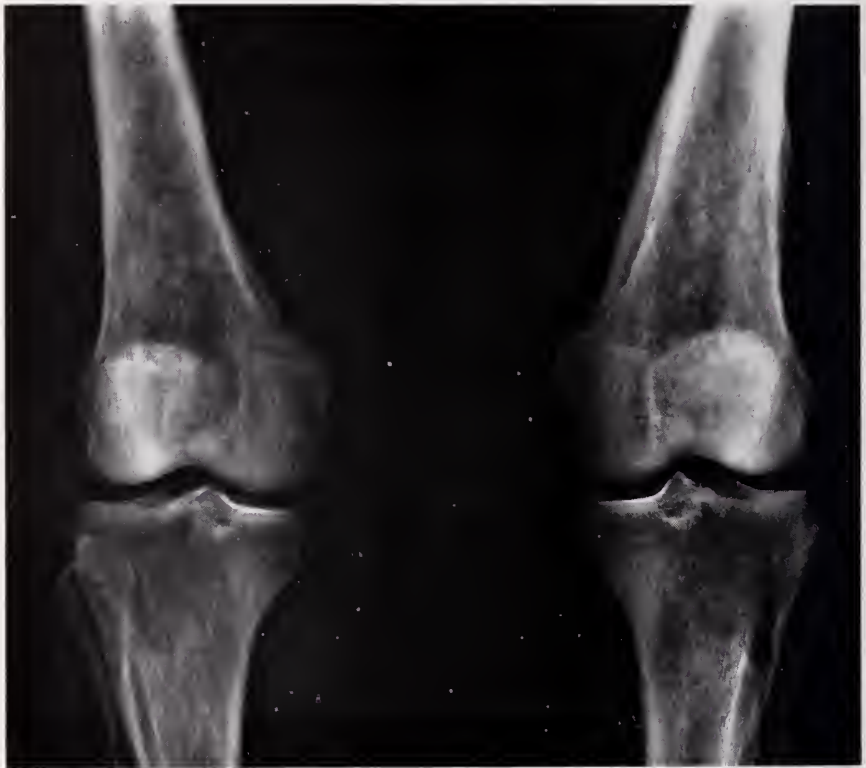


FIG. 25. Myelosclerosis. There is coarse periosteal new bone formation along the distal medial aspects of the femora and the proximal lateral aspects of the tibiae. More minimal periosteal reaction is noted along the lateral aspect of the left femur. There is an increase in the number and thickness of the bony trabeculae and at the distal femora there are irregular areas of bone condensation.

covered in adult life, most often by roentgen examination. It is this benign adult form of osteopetrosis which, on occasion, must be differentiated from myelosclerosis. Such patients, having survived to middle and late life, are frequently asymptomatic. Enlargement of the liver and spleen is distinctly uncommon. Anemia is usually mild or absent. The disorder is familial in at least fifty per cent of the cases. Hinkel and Beiler (20) have given an excellent summary of the findings reported in 25 cases of osteopetrosis in adults.

In this form of the disease the most characteristic finding in the skull is thickening of the posterior clinoids and dorsum sellae. On some occasions the ante-



FIG. 26. Myelosclerosis. There are localized areas of coarse periosteal new bone at the medial aspects of the distal tibiae. The patient was a 65 year old female who had been under observation for myelosclerosis for 9 years. Coarse periosteal new bone was also present along the medial femoral cortices and the lateral aspects of the tibiae at the knees.

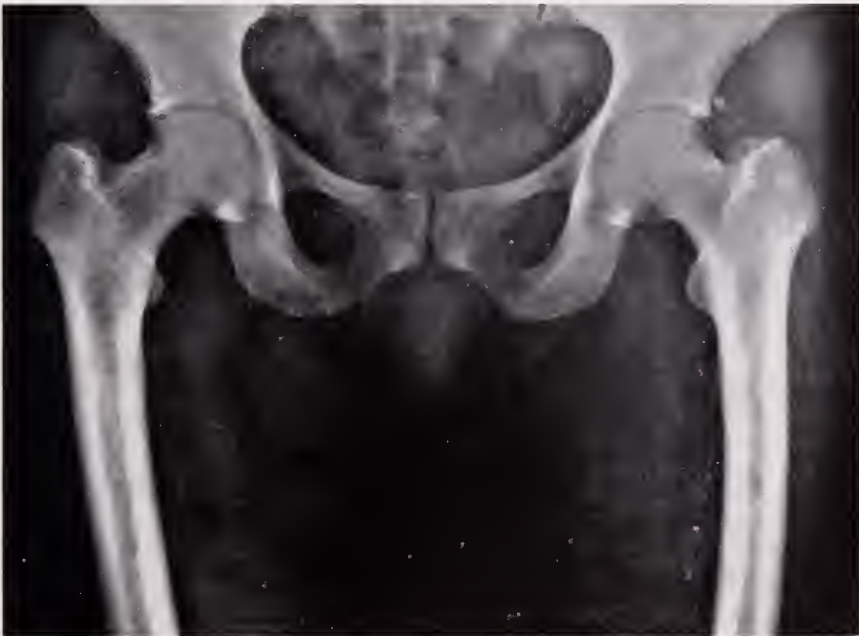


FIG. 27. The cortices of the femoral shafts are thickened on their inner aspects with resultant narrowing of the medullary cavities. There is increased bony structure within the marrow spaces. The changes in the femoral shafts cannot be differentiated from those commonly found in sickle cell disease. The patient was a 60 year old female with myelosclerosis of 5 years duration.



rior clinoids, as well, are sclerotic. In more severe cases the base of the skull may be thickened and the mastoids and sinuses obliterated. Thickening of the cranial vault with obliteration of the diploe may occur. Multiple small areas of lucency such as occur in some cases of myelosclerosis are not seen.

As in myelosclerosis, the spine, pelvis, proximal ends of the humeri and both ends of the femora are sites of frequent involvement. In the spine in adult osteopetrosis, however, there is usually a marked increase in the density of the superior and inferior vertebral plates with relatively normal bone in between. The resulting "sandwich-like" appearance is not seen in myelosclerosis. In the pelvis,

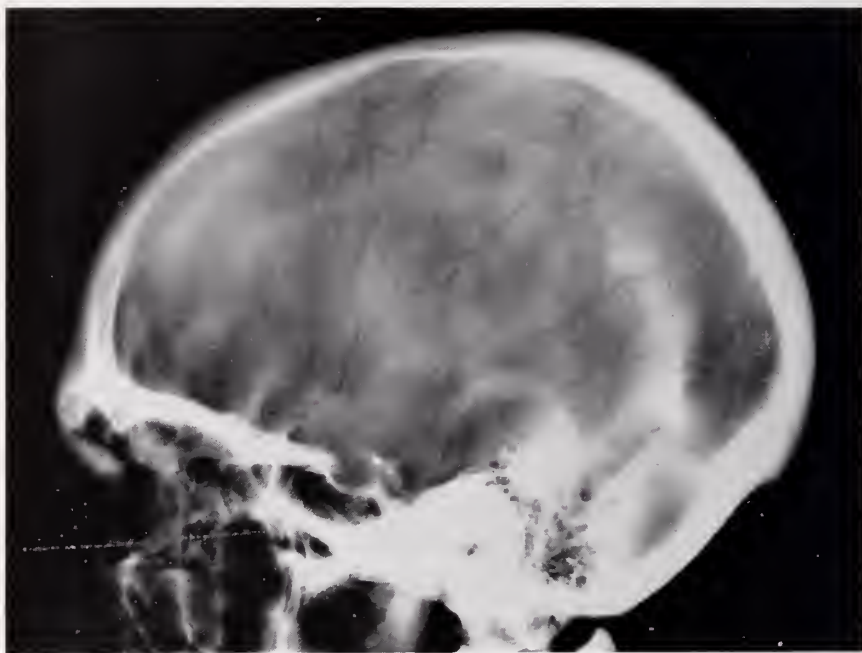


FIG. 28. The diploic space between the tables of the skull is obliterated and the bone is slightly increased in density. The vascular markings are outstanding against the homogeneous background of thickened bone. The patient was a 42 year old female with myelosclerosis of 6 years duration.

carpals and tarsals and sometimes in the ends of long bones there may be a "bone within a bone" appearance or concentric rings of alternating increased and diminished density presumably due to exacerbations and remissions of the disease. This "bone within a bone" appearance is characteristic of osteopetrosis and is never seen in myelosclerosis.

Perhaps more basically, the osteosclerosis in marble bone disease is of greater density, involves predominantly the metaphyseal ends of the long bones, and in these areas is characterized by transverse and longitudinal striations. This is unlike the less intense density of myelosclerosis which is frequently associated with small areas of bone condensation and/or spotty radiolucency. Transverse and longitudinal striations within the sclerotic zones are not seen in myelosclero-

sis. In some cases of adult osteopetrosis, however, the skeletal changes may consist of a generalized diffuse increase in the density of bone with partially obliterated marrow cavities. In such instances localization of sclerotic changes to the metaphyses may be limited to the phalanges, metacarpals and metatarsals.

Osteoblastic metastatic carcinoma, on rare occasions, may present a formidable problem in differential diagnosis. This is particularly so in those cases in which small metastatic blastic lesions are generalized throughout the skeleton. In most cases of osteoblastic metastatic disease, however, the lesions are not

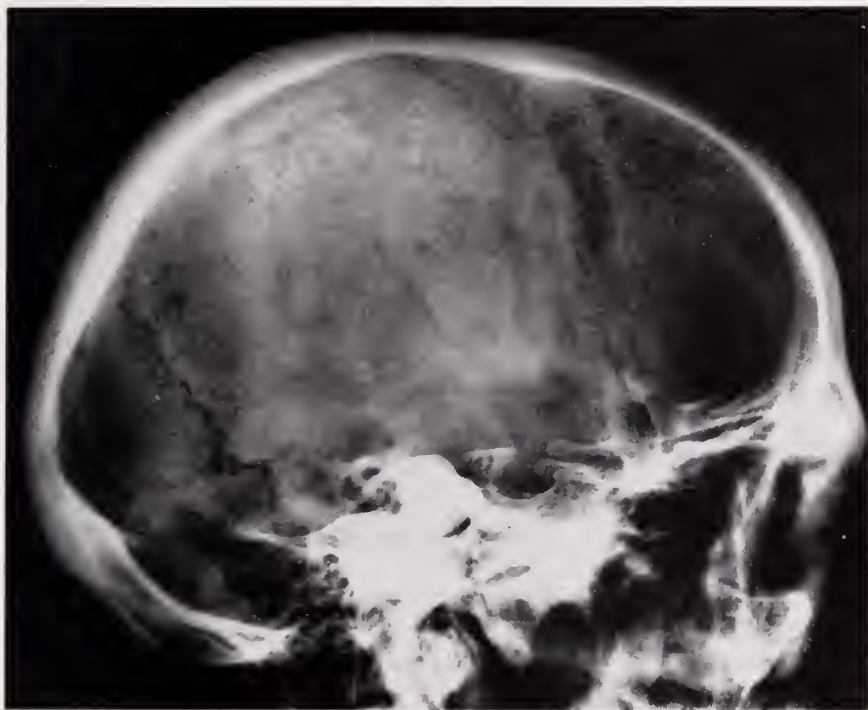


FIG. 29. Myelosclerosis. There are multiple small rounded areas of radiolucency in the parietal and frontal regions of the skull. The bones do not show any significant increase in density.

generalized, nor are they symmetrically distributed. The large spleen in myelosclerosis would also be a significant differentiating factor.

The thickening which may be seen on the inner aspects of the cortices in myelosclerosis is identical to that seen in sickle cell disease. This finding is most confusing when seen at the hips and femora, as the osteosclerosis at the femoral heads and necks may be similar in appearance to the infarctive changes in sickle cell disease (21). To make the differentiation it may be necessary to examine other portions of the skeleton, especially the spine, which is apt to show osteoporosis with cupping in sickle cell disease. Cases of sickle cell disease which may be seen in middle and late life would be the sickle cell-hemoglobin C variant since the vast majority of sickle cell anemia (SS) patients do not survive beyond

the age of 40 and very few of them survive beyond 30 years. If the patient is not a Negro, consideration of sickle cell disease is not a serious one although the rare case of sickle cell-thalassemia should not be overlooked. Since the spleen is frequently enlarged in both sickle cell-C disease and sickle cell-thalassemia, splenomegaly is not a factor in the differential diagnosis.

More nearly identical to the osseous changes in myelosclerosis are the bone abnormalities which are demonstrable in some cases of urticaria pigmentosa (22-24). Bone changes are by no means rare in this mast cell disorder having been found in 21 of 53 cases studied radiographically (24). In several of the reported cases thickened trabeculae with patchy areas of bone condensation and diffuse osteosclerosis with scattered areas of radiolucency are impossible to differentiate radiographically from myelosclerosis. The areas of most frequent involvement are similar to those in myelosclerosis. Thus, the central skeletal segments, spine, pelvis and thorax and the humeri and femora are most often affected. The skull may be involved as well. Mast cell infiltration of the bone marrow is presumably responsible for the osteosclerosis. There may be hepatomegaly, splenomegaly and anemia. Skin manifestations and demonstration of tissue mast cells in bone marrow, splenic aspirates or peripheral blood examination aid in differentiation. Jensen and Lasser (25) caution, however, that mast cells may not be found in the splenic or bone marrow aspirate even when they are present in large numbers in the spleen and marrow as demonstrated by surgical biopsy or post mortem examination.

Most other conditions which produce osteosclerosis do not present serious difficulties in differential diagnosis. In the rare case where the radiographic findings do not permit a differentiation, clinical and laboratory findings must be relied upon for diagnosis and the radiologist can do no more than suggest the possible causes for the roentgen appearance.

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# SURVEY OF PATIENTS WHO HAVE BEEN ATTENDING NON-PsYCHIATRIC OUTPATIENT DEPARTMENT SERVICES FOR TEN YEARS OR LONGER

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One of the results of the closer interrelationship between psychiatry and the other branches of medicine has been, in recent years, the growing number of reports exploring groups of medical and surgical patients from the view point of psychiatric illness (1-8). The establishment of psychiatric units in general hospitals has been an important factor in stimulating and making possible this type of research (9). The present study intends to bring a further contribution to the general subject by presenting the findings of a survey of a large group of patients who have been attending non-psychiatric Outpatient Department (O.P.D.) services for ten years or longer. These patients present problems of which many physicians are aware but to which they have given little attention.

It must be emphasized that a study of the incidence of psychiatric illness among these patients is not the only purpose of our survey. We assumed that the problems presented by these patients have a bearing upon all aspects of medical care and administrative policy. This has led us to investigate the data to arrive at a more thorough evaluation of this category of patients.

This study is an attempt to answer the following and other questions on the basis of the clinical material from the general O.P.D. of The Mount Sinai Hospital of New York:

A. What is the incidence of psychiatric illness among these chronically ill patients? What types of psychiatric conditions are present?

B. What are the patterns of attendance and is there any relationship between the patterns of attendance, the utilization of the O.P.D. facilities and the presence of psychiatric illness?

C. How frequently and how early is a psychiatric illness recognized by the O.P.D. physicians? What is the nature of the doctor-patient relationship?

## MATERIAL AND METHOD

### *Collection of Data*

In 1958 the O.P.D. of The Mount Sinai Hospital of New York provided diagnostic and therapeutic facilities for approximately 20,000 low-income patients. Of these, approximately eight thousand were new admissions in that year. The

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A preliminary report on this subject was read at the 115th Annual Meeting of the American Psychiatric Association, Philadelphia, Pa., April 27-May 1, 1959.

clinic files contain about 2,500 "active"\* records of patients whose first admission falls between 1932 and 1947. For the purpose of the study we have selected at random and reviewed 200 of the 2500 charts. Data were gathered concerning: age, sex, marital status, employment status, number of clinics visited, number of consultations requested, number of laboratory tests performed, number of appointments made and kept, types of non-psychiatric diagnoses, presence of "psychosomatic" diseases, response to treatment and aspects of the doctor-patient relationship. The frequency and types of psychiatric disorders encountered were established. The patients were then classified according to their patterns of attendance in order to determine whether such patterns are related to psychiatric illness and the utilization of the O.P.D. facilities. Interviews were conducted on twenty patients selected at random from among the 200 patients. As an additional group we had selected at random and reviewed fifty records of patients who had been attending the O.P.D. only for the last two years.

Before presenting the results obtained, we wish to outline briefly the method we followed in establishing the presence and the types of psychiatric illness in this study.

### *Presence of Psychiatric Illness*

The presence of psychiatric illness was established in the following manner:

(A) One hundred and twenty-one records contained two or more notes which stated that the patient's complaints or symptoms were related to or caused by an emotional disturbance. Not infrequently the opinion of the O.P.D. physicians was formulated in a specific psychiatric diagnosis such as "anxiety neurosis," "psychoneurosis," "neurasthenia" or "psychopathy." Sixty-five of these 121 records also showed a psychiatric evaluation made by the consultant psychiatrist.

(B) The remaining records contained no diagnosis or impression. However, 26 records contained elements which strongly suggested that a psychiatric factor was in operation. These elements may be summarized as follows: (1) Presence of complaints which, although not pathognomonic, are common in psychiatric disorders: dizziness, nervousness, irritability, loss of sleep and appetite, apprehension, easy fatigability, weakness, palpitations and gastric distress. The complaints were frequently characterized as "vague." (2) The lack of a medical diagnosis and the absence of physical findings and laboratory reports which could account for the above described complaints. (3) The course of the illness; this usually remained stationary with fluctuation of symptoms but no further development of physical signs over a long period of time. In other cases, the improvement or sudden disappearance of often severe complaints following prescription of aspirin or a mild sedative, was interpreted by us as an indication of possible psychogenic factors. Fluctuation in the patient's condition were, at times, related to psychologically traumatic events in the patient's life by the

\* A record is considered "active" if continued absence of a patient from the O.P.D. does not extend over four years.

o.p.d. physicians themselves (4). The label of "chronic complainer" was frequently given to these patients.

Although we are aware of the limitations of some of these criteria in the evaluation of the presence of a psychiatric disorder, we wish to emphasize that we did not reach this conclusion unless there was a combination of the first three elements just described.

### *Types of Psychiatric Illness*

Except for those cases in which a diagnosis was made by the psychiatric consultant or by us in the personal interviews, all diagnoses must be considered as "tentative." The possibility that seemingly psychoneurotic symptoms and various somatic manifestations might have been expression of illnesses with a different etiology is certainly to be kept in mind (10). Under the heading of "psychoneurosis" we included both fairly transient neurotic reactions and long-standing cases of character neurosis. Under the heading of "organic brain disease" we included five patients whose psychiatric symptoms had begun late in life and were considered to be related either to arteriosclerosis, senility, or both. This also included one patient whose mental picture was due to myxedema. Under the heading of "psychiatric disease, undiagnosed" were cases seen by the psychiatric consultant and left undiagnosed.

## RESULTS

### *Frequency and Types of Psychiatric Illness*

As already mentioned, 121 records contained a psychiatric diagnosis and in 26 additional records we found sufficient symptomatological evidence to justify a psychiatric diagnosis on our part according to the criteria enumerated above. In total, 147 (73.5%) patients of the 200 studied were found to have a psychiatric illness. The frequency and types of psychiatric illnesses found are summarized in Table I. We wish to draw attention to the fact that the number of schizophrenic patients in our sample is eight (4%). This percentage is about four times the estimated incidence of schizophrenia in the general population (11). Kaufman *et al.* also found a high percentage of schizophrenic patients in their study of psychiatric findings in admissions to the medical service of a general hospital (2).

### *Patterns of Attendance*

These were established by taking into consideration the frequency of the appointments, the length of the intervals between clusters of visits and the length of time during which a patient was attending the o.p.d. for the same type of complaints.

Two groups of patients could thus be distinguished:

Group 1. Patients who had been attending the o.p.d. regularly with very short intervals between visits. This group comprises 168 patients (84%).

Group 2. Patients who had attended the o.p.d. following the onset of acute illnesses or the exacerbations of chronic conditions and had long intervals of



continued absence from the clinic. It seems that these patients used the o.p.d. similarly to private patients who seek the assistance of their family physician. This group consists of 32 patients (16%).

*Relationship between Patterns of Attendance and  
Utilization of O.P.D. Facilities*

The patient whose attendance was uninterrupted visited a significantly greater number of different clinics, had a greater number of consultations and laboratory tests performed and, as expected, had a greater number of appointments than the patient whose attendance was marked by long intervals of absence.

TABLE 1  
*Frequency and Types of Psychiatric Illnesses*

Classification	Number and Per Cent of Patients
A. Psychoneurosis .....	121 (60.5%)
B. Functional psychosis .....	
Schizophrenia .....	8 (4%)
Manic depressive psychosis .....	1 (0.5%)
Involucional melancholia .....	1 (0.5%)
All functional psychoses .....	10 (5%)
C. Organic brain disease .....	6 (3%)
D. Mental defective .....	1 (0.5%)
E. Psychiatric disease, undiagnosed .....	9 (4.5%)
Total with psychiatric disease .....	147 (73.5%)
Total without psychiatric disease .....	53 (26.5%)

*Relationship between Patterns of Attendance and  
Presence of Psychiatric Illness*

Of the 168 patients (Group 1) with regular attendance, 132 (78.5%) had a psychiatric illness. Of the 32 patients (Group 2) with irregular attendance 15 (47.8%) had a psychiatric illness. The difference between the two percentages is significant at the .01 level of confidence indicating the relationship between continuous attendance and psychiatric disturbance.

*Relationship between Psychiatric Illness and  
the Utilization of O.P.D. Facilities*

Groups 1 and 2 will be considered separately:

GROUP 1 (Patients with a regular attendance). Evaluation of the 168 patients comprising this group showed that, although they had the same pattern of attendance, they could be separated into three different subgroups on the basis of the relationship between the psychiatric and the medical diagnosis.

*Subgroup A.* This group was composed of 32 of the 168 patients (19.2%) in which the primary diagnosis was a psychiatric one.

*Subgroup B.* This group was composed of 89 patients (53%) in which both a

psychiatric and a medical and/or surgical condition played an equally important role.

*Subgroup C.* This group was composed of 47 patients (27.8%) in which the primary diagnosis was a chronic medical illness which required constant attention (such as diabetes, hypertensive vascular disease and epilepsy). Eleven of these 47 patients also had a psychiatric illness, which was either organic such as a late complication of arteriosclerosis or a very fleeting neurotic reaction which did not seem to have a bearing on the course of the illness and the attendance.

The three subgroups, A, B and C, may be compared in the utilization of the O.P.D. facilities:

TABLE II

*Number of Clinics Visited by Patients of Group I (patients with continuous attendance)*

Subgroups	Patients	Mean Number of Clinics Visited
A. Primary diagnosis—psychiatric.....	32	8.0
B. Primary diagnosis—combined psychiatric and medical/surgical.....	89	8.1
C. Primary diagnosis—chronic medical/surgical illness.....	47	5.0

TABLE III

*Frequency and Results of Consultations for Patients of Group I (patients with continuous attendance)*

Subgroups	Mean Number of Consultations	Mean Number of Consultations With Negative Results	Number of Patients Who Did Not Receive Consultations
A. Primary diagnosis—psychiatric.....	6.0	3.2	0
B. Primary diagnosis—combined psychiatric and medical/surgical.....	4.7	1.9	2
C. Primary diagnosis—chronic medical/surgical illness.....	1.7	0.8	12

A. Clinics Visited. Table II illustrates the mean number of different clinics visited by patients of subgroups A, B and C. The difference between the means of A and B on one hand and C on the other is significant at the .01 level of confidence. This finding corroborates our impression in reviewing the records; patients with psychiatric illness are more likely to develop complaints and symptoms of a multiple nature, which in turn leads to referrals to several different clinics.

B. Consultations. Table III illustrates the mean number of consultations received by these patients, the mean number of consultations which proved to be negative and the total number of patients for each subgroup who received no consultations at all.

In regard to the number of consultations, the difference between the mean of

Subgroup A and the mean of Subgroup B is not significant. However, the difference between either of the means of A and B and the mean of C is significant at less than the .01 level of confidence. This latter finding signifies the larger number of consultations undertaken in patients with psychiatric difficulties and is in accordance with the observation of Sheppard *et al.* They also reported that "psychiatric" patients found in general practice averaged nearly double the number of consultations, compared with the remaining patients (7).

In regard to the number of consultations with negative findings, the A patients reached the highest number and the B patients who had multiple diagnoses (*v. infra.*) had proportionately the lowest number of negative results.

It is also significant that no patient in Subgroup A and only two patients in Subgroup B went through their attendance without receiving a consultation. This should be compared with twelve patients in Subgroup C.

C. Laboratory Tests. Table IV shows the mean number of laboratory tests performed and the percentage of tests which yielded no positive results.

TABLE IV  
*Frequency and Results of Laboratory Tests for Patients of Group I*  
(patients with continuous attendance)

Subgroups	Mean Number of Laboratory Tests Performed	Per Cent of Laboratory Tests with Negative Results
A. Primary diagnosis—psychiatric.....	27.5	85.7
B. Primary diagnosis—combined psychiatric and medical/surgical.....	21.	76.2
C. Primary diagnosis—chronic medical/surgical illness.....	15.5	52.8

The difference between the mean of Subgroup A and the mean of Subgroup C is significant at less than the .01 level of confidence. The difference between the means of Subgroups A and B and between the means of Subgroups B and C is significant at the .05 level of confidence. The differences between the percentages of the tests with negative results are all significant at less than the .01 level of confidence.

These findings show: (1) that patients with psychiatric illness tend to have more laboratory tests than patients with primary medical illnesses and (2) that the more predominant the psychiatric disability, the greater the percentage of negative laboratory tests, indicating the important role of hypochondriacal and "functional" symptoms which may puzzle the physician and lead to the utilization of the laboratory in an attempt to discover some organic disease (1, 12).

D. Appointments Made and Kept. The mean number of appointments made and kept is shown in Table V.

The patients of Subgroup A made and kept a significantly higher (.05 level of confidence) number of appointments than the patients of the other two subgroups. A very high percentage of the appointments made were kept (about 90%) with very little variation between the groups in this respect.

E. Non-psychiatric Diagnoses. We include here only the diagnoses made by the physicians of the clinics most frequently attended by each patient. Tables VI-VIII illustrate the number and types of non-psychiatric diagnoses. With the

TABLE V  
*Frequency of Appointments Made and Kept for Patients of Group I*  
(patients with continuous attendance)

Subgroups	Mean Number of Yearly Appointments Made	Mean Number of Yearly Appointments Kept
A. Primary diagnosis—psychiatric .....	17.5	15.5
B. Primary diagnosis—combined psychiatric and medical/surgical .....	12.7	11.1
C. Primary diagnosis—chronic medical/surgical illness.....	10.1	9.3

TABLE VI  
*Number and Types of Nonpsychiatric Diagnoses for Patients of Subgroup A (32 patients; Primary Diagnosis: Psychiatric)*

System Involved	Number and Type
Respiratory .....	2 (1 bronchitis, 1 rhinitis)
Gastrointestinal .....	3 (1 diverticulosis, 2 spastic colon)
Musculoskeletal .....	14 (9 osteoarthritis, 2 sciatica, 2 tenosynovitis, 1 bursitis)
Skin .....	6 (2 eczema, 1 neurodermatitis, 1 dermatophytosis, 1 lichen simplex, 1 herpes zoster)
Cardiovascular and peripheral vascular .....	4 (1 paroxysmal tachycardia, 3 hemorrhoids and varicose veins)
Endocrine .....	3 (1 hypothyroidism, 1 hyperthyroidism, 1 thyroid adenoma)
Neurological .....	1 (Parkinson's Disease)
Urogenital and gynecological .....	9 (5 "menopausal syndrome", 2 vaginitis, 1 ovarian tumor, 1 "stress incontinence.")
Eye and ear .....	1 (acute conjunctivitis)
Hematopoietic .....	4 (mild secondary anemia)
Metabolic .....	1 (diabetes)
Allergy .....	3 (2 asthma, 1 hay fever)
Total number of diagnoses .....	51

exception of allergic and metabolic diseases, the diagnoses are grouped according to the systems involved.

These findings deserve closer scrutiny and will be discussed presently. An evaluation of the total number of non-psychiatric diagnoses and the mean number for each group is shown in Table IX. The mean number of diagnoses of Subgroup B is significantly higher (.01 level of confidence) than either mean of

Subgroups A and C. The B patients constitute slightly more than half of the group of 168 patients with continuous attendance and are responsible for slightly more than  $\frac{2}{3}$  of the diagnoses in this group. This finding can be usefully compared with that of Hinkle and Wolff, who investigated the illness experience

TABLE VII

*Number and Types of Nonpsychiatric Diagnoses for Patients of Subgroup B (89 patients; Primary Diagnoses—Psychiatric and Medical/Surgical)*

System Involved	Number and Type
Respiratory.....	22 (4 bronchitis, 3 pneumonitis, 11 sinusitis, 1 emphysema, 2 pharyngitis, 1 rhinitis)
Gastrointestinal.....	27 (8 gallbladder disease, 6 anal fissure, 4 peptic ulcer, 2 ulcerative colitis, 2 mucous colitis, 1 gastroenteritis, 1 carcinoma of rectum, 1 diverticulosis, 1 carcinoma of stomach, 1 hernia)
Musculoskeletal.....	62 (45 osteoarthritis, 10 bursitis, tenosynovitis, myositis, 2 spondylitis, 3 lumbosacral neuralgia, 1 fracture, 1 rheumatoid arthritis)
Skin.....	24 (6 neurodermatitis, 4 alopecia areata, 2 dermatophytosis, 3 eczema, 3 dermatitis, 3 lichen simplex, 2 angioneurotic edema, 1 herpes zoster)
Cardiovascular and peripheral vascular.....	33 (1 rheumatic heart disease, 17 hypertensive vascular disease, 1 "organic heart disease," 1 aortic aneurysm (Lues), 15 varicose veins and hemorrhoids, 3 thrombophlebitis, 1 Raynaud's)
Endocrine.....	4 (3 thyroid adenoma, 1 thyrotoxicosis)
Neurological.....	4 (1 Parkinson's, 1 Bell's Palsy, 1 trigeminal neuralgia, 1 epilepsy, 1 cerebral arteriosclerosis)
Urogenital and gynecological.....	65 (23 menopausal syndrome, 9 fibroma, 17 infection, 5 cystocele, 3 fistula, 2 ovarian cysts, 6 cervical polyps and erosion)
Eye and ear.....	5 (3 otitis, 1 Menière syndrome, 1 conjunctivitis)
Hematopoietic.....	2 (secondary anemia)
Breast.....	2 (1 chronic cystic disease, 1 abscess)
Metabolic.....	14 (11 diabetes, 3 hypercholesterolemia)
Allergy.....	14 (6 asthma, 7 hay fever, 1 urticaria)
Tentative diagnosis and no diagnosis.....	21
Total number of diagnoses.....	306

of 3500 people and found that  $\frac{1}{4}$  of the group was responsible for  $\frac{2}{3}$  of the illnesses, and that clusters of illnesses tended to occur more frequently in individuals who had difficulty in adaptation to the environment and life situations (13). The difference between these authors' figures and ours is probably that they included psychiatric illness in the evaluation of their patients. (If we add psychiatric diagnoses in our sample the B patients would be responsible for



well over  $\frac{2}{3}$  of the total number of diagnoses.) In addition, Hinkle and Wolff deal with a sample of the general population while our group is by definition, representative of a "sick" population. Findings similar to those of Hinkle and

TABLE VIII

*Number and Types of Nonpsychiatric Diagnoses for Patients of Subgroup C  
(47 patients: Primary Diagnosis—Chronic Medical/Surgical Disease)*

System Involved	Number and Type
Respiratory.....	4 (1 TBC, 1 bronchitis, 1 rhinitis, 1 sinusitis)
Gastrointestinal.....	4 (1 liver cyrrhosis, 1 esophageal diverticuli, 1 Ca. of stomach, 1 G.B. disease)
Musculoskeletal.....	17 (1 shoulder dislocation, 1 Paget's disease, 1 bursitis, 2 bone neoplasm, 12 osteoarthritis)
Skin.....	8 (4 Lues, 1 cyst, 1 psoriasis, 1 eczema, 1 neuro-dermatitis)
Cardio-vascular and peripheral vascular.....	19 (23 A.S.H.D. 1 Lues, 4 varicose veins, 1 T.A.O., 1 Raynaud's)
Endocrine.....	3 (1 Addison's, 1 myxedema, 1 hypoparathyroidism)
Neurological.....	5 (3 epilepsy, 1 cord neoplasm, 1 trigeminal neuralgia)
Urogenital.....	2 (1 cystitis, 1 prostatic hypertrophy)
Eye and ear.....	4 (2 chronic conjunctivitis, 1 glaucoma, 1 cataract)
Hematopoietic.....	1 (Hodgkin's disease)
Breast.....	2 (carcinoma)
Metabolic.....	9 (diabetes)
Allergy.....	7 (5 asthma, 2 allergic rhinitis)
Total number of diagnoses.....	85

TABLE IX

*Total and Mean Number of Nonpsychiatric Diagnoses for Patients of Subgroups A, B and C in Group I (patients with continuous attendance)*

Subgroups	Total Number of Nonpsychiatric Diagnoses	Mean Number of Nonpsychiatric Diagnoses
A. Primary diagnosis—psychiatric.....	51	1.6
B. Primary diagnosis—combined psychiatric and medical/surgical.....	306	3.4
C. Primary diagnosis—chronic medical/surgical illness.....	85	1.8

Wolff are also reported by Buck and Hobbs (14) and by Rees (15). In contrast to the B patients, the C patients whose primary diagnosis is a medical one, compose less than  $\frac{1}{4}$  of the group and are responsible for less than  $\frac{1}{5}$  of the total number of diagnoses. The A patients whose primary diagnosis is a psychiatric one compose less than  $\frac{1}{3}$  of the group and are responsible for less than



$\frac{1}{8}$  of the total number of the diagnoses. This latter finding is of interest especially in association with the large number of clinics visited and with the very many consultations undertaken; similarly, negative laboratory results and appointments made reached the highest figures in this group. It must also be noted that relatively few of the non-psychiatric diagnoses among the A patients refer to illnesses of a nature requiring constant and prolonged attendance. One case of diabetes and one case of Parkinson's disease developed quite late in two patients who had already attended the O.P.D. for more than ten years. It would seem, therefore, that the two groups of patients with psychiatric illness (A and B) show quite different pathological profiles. In fact, even though both groups showed a very large number of consultations, clinics visited and negative laboratory data, the A patients tended to develop multiple complaints, but received relatively few diagnoses, and the B patients actually tended to develop multiple somatic diseases. For both groups it may be said that the high rate of utilization

TABLE X

*Frequency and Types of "Psychosomatic Diseases" in Patients of Group I (patients with continuous attendance)*

Subgroups	Hypertension	Ulcerative Colitis	Mucous Colitis	Spastic Colon	Peptic Ulcer	Rheumatoid Arthritis	Neurodermatitis	Alopecia Areata	Asthma	Total
A. Primary diagnosis—psychiatric.				2			1		2	5
B. Primary diagnosis—combined psychiatric and medical/surgical	17	2	2		4	1	5	4	6	41
C. Primary diagnosis—chronic medical/surgical illness	12						1		5	18

of the O.P.D. facilities is also an indication of the puzzling nature of many symptoms shown by these patients (1, 2). Another relevant finding was that certain illnesses (*i.e.*, diabetes and osteoarthritis) were considered in most cases to be of mild or moderate degree for A and B patients and "severe" for C patients. We also found that the gynecological clinic was frequently attended by A and B patients but not by the C patients.

F. Psychosomatic Illnesses. We included under this heading only few entities in which the psychophysiological correlation is thought to be particularly significant and which are classified as such by many workers. Subgroup B contains the highest proportion of "psychosomatic" illnesses. Peptic ulcer and ulcerative colitis were found only in this group. "Psychosomatic" skin diseases were also frequently diagnosed in Subgroup B. Asthma, however, showed no preference for this group. (See Table X.)

In view of the findings just discussed which show that a patient group with psychiatric manifestations has a large number of different somatic ailments, the concept of "psychosomatic disease" could be enlarged to include a wide variety of illnesses and its descriptive usefulness might therefore become ques-

tionable. We feel, therefore, that it is more appropriate to hold the concept of "psychosomatic medicine" as an "operational approach to the theory and practice of medicine" which includes the study of psychological as well as other factors in the multiple causation of disease (16).

We did not consider conditions such as "gastric neurosis" or "cardiac neurosis" as "psychosomatic", but instead as somatic manifestations of psychoneurotic reactions.

GROUP 2. (Patients with irregular attendance.) Evaluation of the 32 patients forming this group showed that 15 of them (47.8%) had a psychiatric diagnosis. Thirteen were diagnosed by the o.p.d. physicians and the psychiatric consultants and only three were diagnosed solely on the basis of the record by us. Among the 15 psychiatric patients there were 11 who had other significant

TABLE XI  
*Number of Clinics Visited by Patients of Group II*  
(discontinuous pattern of Clinic attendance)

Subgroups	Mean Number of Clinics Visited
Nonpsychiatric (17 patients).....	2.0
Psychiatric (15 patients).....	2.9

TABLE XII  
*Frequency and Results of Consultations for Patients of Group II*  
(discontinuous pattern of Clinic attendance)

Subgroups	Mean Number of Consultations Performed	Mean Number of Consultations With Negative Results	Number of Patients Who Did Not Receive Consultations
Nonpsychiatric (17 patients).....	0.6	0.5	14
Psychiatric (15 patients).....	1.7	0.6	3

medical illnesses together with a psychiatric disturbance and four who presented symptoms and complaints only of a psychiatric nature. These were all labeled as "anxiety reactions" or "anxiety states". Because of the small sample, patients with a psychiatric illness were treated as one group, whether the psychiatric diagnosis was primary or not. Psychiatric and non-psychiatric patients with an irregular attendance will be compared now in the utilization of the o.p.d. facilities.

A. Clinics Visited. Table XI shows the mean number of clinics visited by patients who had irregular attendance. Although psychiatric patients attended a somewhat higher number of different clinics there is no significant difference, in this respect, between them and the non-psychiatric patients.

B. Consultations. Table XII shows the mean number of consultations received by patients in Group 2, the mean number of consultations with negative results and the total number of psychiatric and non-psychiatric patients who received

no consultation at all. The difference between the means is significant at the .05 level of confidence. In only three of the psychiatric patients there was no request for any consultation, compared to the 14 patients in the non-psychiatric group.

C. Laboratory Tests. The frequency and the results of the laboratory tests for patients of Group 2 are shown in Table XIII. The differences of the means and the percentages are significant at less than the .01 level of confidence. The percentage of negative laboratory results in this group of non-psychiatric patients is much higher than in the comparable group of patients with continuous attendance (patients of Subgroup C). This difference depends on the fact that the majority of the laboratory tests performed in this group of patients with discontinuous attendance, were routine tests and relatively few special tests were carried out.

D. Appointments Made and Kept. Altogether, the 32 patients attended the O.P.D. for an average of 2.3 times a year. (The average number of appointments made was 2.5 times a year.) There was no significant difference between the psychiatric and the non-psychiatric patients in this respect.

TABLE XIII  
*Frequency and Results of Laboratory Tests for Patients of Group II*  
(discontinuous pattern of Clinic attendance)

Subgroups	Mean Number of Laboratory Tests Performed	Per Cent of Laboratory Tests With Negative Results
Nonpsychiatric (17 patients).....	1.9	63
Psychiatric (15 patients).....	8.2	85

E. Non-psychiatric Diagnoses. A total of 85 diagnoses was made in this group; four diagnoses were considered to be "tentative", in two instances no diagnosis was made; three of the "tentative" diagnoses and the two instances without diagnosis occur in the group of the 15 psychiatric patients; and 20 of the diagnoses made referred to chronic illnesses such as diabetes (always considered mild and not requiring insulin treatment in this group), hypertensive vascular disease, osteoarthritis and asthma. Of these 20 diagnoses, 14 fell into the group of 17 non-psychiatric and 6 into the group of 15 psychiatric patients. There was no evidence of marked clustering of illnesses in this group of patients. However, three patients who received from six to eight diagnoses each had a definite psychiatric disorder.

F. Psychosomatic Illnesses. A total of four "psychosomatic" illnesses was found in this group. There were two cases of peptic ulcer, one in a psychiatric and one in a non-psychiatric patient. One case of asthma was diagnosed in a non-psychiatric patient.

#### *Response to Treatment*

In regard to the 200 patients, the clinic records contained the physicians' evaluation of the patients' response to treatment. The records of the patients

with continuous attendance had a significantly higher (.01 level of confidence) proportion of evaluations indicating poor response to treatment, when compared to patients with discontinuous attendance. Within the same group, patients who had a psychiatric illness showed a significantly higher (.01 level of confidence) proportion of poor response as compared to patients without psychiatric illness.

Sedatives and tranquilizers were also prescribed in a proportionately higher number to patients with a psychiatric disorder. The six patients (3%) who received placebo were psychiatric patients.

TABLE XIV  
*Analysis of Age Distribution*

Group 1	Yrs. 13-30	Yrs. 31-60	Yrs. 61-68
A. Primary diagnosis—psychiatric.....	4 (12.5%)	28 (87.5%)	0
B. Primary diagnosis—combined psychiatric and medical/surgical.....	12 (13.5%)	76 (85.4%)	1 (1.1%)
C. Primary diagnosis—chronic medical/surgical illness.....	12 (25.5%)	26 (55.3%)	9 (19.2%)
Group 2 (32 patients).....	13 (40.6%)	16 (50.0%)	3 (9.4%)

TABLE XV  
*Analysis of Sex Distribution for the 200 Patients*

(The per cent figures are related to the number of patients in each group or subgroup.)

Group 1	Males	Females
A. Primary diagnosis—psychiatric.....	10 (31.2%)	22 (66.8%)
B. Primary diagnosis—combined psychiatric and medical/surgical .....	11 (12.4%)	78 (87.6%)
C. Primary diagnosis—chronic medical/surgical illness.....	20 (62.5%)	27 (57.5%)
Group 2 (32 patients).....	12 (37.5%)	20 (62.5%)

*Relationship of Psychiatric Illness and of Patterns of Attendance to Age, Sex, Occupation and Marital Status*

A. Age. Age at the time of admission is considered. Distributing our sample by decades, the median age is approximately 40 while the range is from 13 to 68 years (See Table XIV). In Subgroups A and B there was a relatively smaller number of patients under the age of thirty or above the age of sixty. This observation is in accordance with the finding that the majority of psychiatric illnesses was found in individuals who were in the fourth and fifth decade at the time of admission to the O.P.D.

B. Sex. The 200 patients comprising the sample had the following sex distribution: 52 (26%) males and 148 (74%) females. Table XV illustrates sex



distribution according to the various groups and subgroups. The significantly higher (.01 level of confidence) number of female patients in Subgroups A and B is indicative of the fact that, in our material, psychiatric diagnoses were made more frequently in female than in male patients.

C. Occupation. Of the patients comprising the sample, 47.5 per cent were housewives, 27.5 per cent were employed (mostly unskilled workers), 14.5 per cent were unemployed and 10.5 per cent were attending school. There was no significant relationship between occupation and psychiatric illness or pattern of attendance.

D. Marital Status. Marital status at the time of admission was considered; 20.5 per cent of the 200 patients were single, 55 per cent married, 11.5 per cent separated, 1 per cent divorced and 11.5 per cent widowed. For one patient marital status was not known. Except for the finding that marital separation was found more frequently among psychiatric patients, the data were not remarkable.

*Frequency with which a Psychiatric Diagnosis was Made  
by the O.P.D. Physician*

The O.P.D. physician recognized the presence of a psychiatric disturbance in 121 (82.5%) out of the 147 cases with a psychiatric diagnosis. In approximately 50 per cent of the cases the psychiatric disorder was diagnosed within three years from the time of admission and in the remaining 50 per cent after three years from the time of admission. There was no appreciable difference between these two groups in terms of the overall patterns of attendance and utilization of the O.P.D. facilities. In most cases the establishment of a psychiatric diagnosis was not followed by a reduction in the number of consultations requested or laboratory tests performed.

*Doctor-Patient Relationship*

Judging from the physician's notes, patients with a psychiatric illness, especially those with continuous attendance, were seen by the O.P.D. physicians as very dependent individuals with a "whining, demanding" and "helpless" attitude, using the O.P.D. facilities mainly because of their emotional needs.

The records of these patients contained frequent remarks of the following kind: "This patient is a chronic complainer;" "Now he complains of pain in the back;" "Nothing makes him feel any better;" "This patient is upset by all sorts of things;" "This patient has child-like pleasure in coming to the clinic and telling the doctor all her troubles;" "This patient is not a 'cardiac' (or 'orthopedic,' or 'gynecological' or 'gastrointestinal') patient; he should not come back to this clinic." This latter remark was often made after the patient had already attended the special clinic for several times. The doctors' attitude toward these patients appeared to be simultaneously one of irritation and passive tolerance. It seemed to us that the tendency to frequently refer the patients to another clinic or for consultation was the result partly of the ambivalent attitude of the O.P.D. physicians and partly of the previously mentioned marked tendency of these patients to develop multiple and puzzling complaints or actual multiple somatic



diseases. It seemed reasonable for us to assume, in this respect, that the change of physicians over the years might have been an additional cause for the lack of a more holistic approach to the problems of these patients.

The findings related to the number of consultations and laboratory reports can also be seen under two different aspects: (a) It is of interest to note that no important disease was overlooked and in no instance were symptoms labeled "functional" which later turned out to be of organic nature. This, signifies good medical care; (b) On the other hand, the frequent referrals for consultations and laboratory tests might increase the already strong tendency toward "symptom fixation" and thus facilitate regressive behavior in these patients.

#### *Evaluation of Patients who Received Psychiatric Attention*

Sixty-five (32.5%) of the 200 patients were referred for psychiatric consultation. We thought it would be of interest to see how many of the psychiatric referrals had been made within three years from the time of admission and how many after this period, in order to ascertain whether the time of recognition of a psychiatric disturbance would have any bearing on the results of treatment. We found that the referrals were almost equally divided between these two periods of time. We related the "early" and "late" referrals to the response to treatment and found no significant difference, although there was a slight tendency in the "early" referrals group to respond better to the treatment.

Of the 65 patients referred for a psychiatric consultation, 40 patients attended the psychiatric clinic for variable lengths of time; 17 of them were A patients, 20 B patients, 1 a C patient and 2 came from the group of discontinuous attendance. We also found that among the "early" referrals for psychiatric consultation there were 23 patients who attended the psychiatric o.p.d., 17 of them for one year or more. Among the "late" psychiatric referrals there were 17 who attended the psychiatric o.p.d., 8 of them for one year or more. This evidence would suggest that "early" referrals tended to receive psychiatric treatment more often and for a longer period of time than "late" referrals.

In terms of response to psychiatric treatment, an evaluation of the psychiatric clinic charts revealed five favorable responses in the group of "early" referrals and three favorable responses in the group of "late" referrals. Also in the "early" referral group were four patients (two cases of ambulatory schizophrenia and two of psychoneurosis) who, while attending the psychiatric o.p.d. attended other clinics to a considerably lesser degree. There were two such cases (both psychoneurosis) in the "late" referral group.

Treating the forty patients who had attended the psychiatric o.p.d. as a separate group and analyzing the data pertaining to them, we failed to see any significant difference in patterns of attendance and utilization of the o.p.d. facilities between this group and the A and B groups. A review of the psychiatric records suggests that the type of psychiatric treatment that these patients were offered, with emphasis on insight and interpretation and relative lack of concern for their somatic complaints, was not perhaps the most suitable. As our figures show, the attendance to the psychiatric clinic was, for most patients, either a

very brief and probably insignificant experience, or it meant another clinic where another doctor would listen to the endless list of complaints.

#### THE CONTROL GROUP

We selected at random and reviewed fifty charts of patients who have been attending the non-psychiatric O.P.D. services for the last two years only. This was an attempt to establish how early in the course of attendance to the O.P.D. some of the trends found in the group of patients studied would become apparent. We found that nine patients (18%) attended the O.P.D. a few times only, had specific medical problems, responded favorably to treatment and then stopped coming to the clinic. These patients can be compared to the "non-psychiatric" patients of Group 2 of the main sample and are significantly more numerous (.01 level of confidence) in the control than in the main group. The bulk of the control group was composed of 27 patients (54%) with chronic medical illnesses requiring constant care. The number of these patients is also significantly higher (.01 level of confidence) in the control than in the main group. Fourteen patients (28%) had records which contained a definite psychiatric diagnosis. In seven cases the psychiatric diagnosis had been made by the O.P.D. physicians only and in seven cases there was, in addition, an evaluation by the psychiatric consultant. In no case of the control group was the diagnosis made solely on the basis of our impression from the records. In the control group, we were able to distinguish one group of eight patients whose primary diagnosis was a psychiatric one and one group of six patients in whom both a psychiatric and a medical condition had played an equally important role.

The outstanding finding is the relatively low proportion of patients with psychiatric illness in the control group when compared with the main group (level of significance .01). This would suggest that patients whose primary diagnosis is a medical one tend to drop out from the O.P.D. and their place tends to be taken by patients with psychiatric illness, whose number becomes increasingly higher as the length of attendance also increases. However, the finding that a sample of patients attending the O.P.D. for two years only contains 28 per cent of patients with psychiatric disturbances, in itself indicates the important role played by psychiatric disorders in a general O.P.D. population.

We investigated the utilization of the O.P.D. facilities in the control group and related it to the patterns of attendance and to the presence of psychiatric illness, applying the same method as in the main group. Because of the small number, patients with a psychiatric illness were treated as one group, whether the psychiatric diagnosis was the primary diagnosis or not. Similar to what we had found in the main sample of 200 patients, in the control group too, the number of clinics visited, appointments, consultations, laboratory tests and negative laboratory results, were significantly higher (levels of significance ranging from .01 to .05) in the patients with psychiatric illness. It must be noted, however, that with the exception of the number of appointments per year, the figures relating to the utilization of the various O.P.D. facilities were considerably lower in the control than in the main group. This finding would suggest that the tend-

ency to attend several clinics and to receive a large number of consultations and laboratory tests increases in direct proportion with the length of attendance.

An analysis of the psychiatric diagnosis in the control group reveals that there were eleven cases of psychoneurosis, one of schizophrenia, and two of involutional psychosis.

The group was composed of 36 women (72%) and 14 men (28%). There was, therefore, no significant difference in this respect with the main group. Women were predominant in the group with psychiatric manifestations. The age ranged from 14 to 75 years; the median age was approximately 45 years. Patients with psychiatric illness were more often in the fourth and fifth decade at the time of admission. This is probably due to the fact that most cases with psychiatric diagnoses were of women who developed neurotic reactions in coincidence with the menopause.

#### INTERVIEWS WITH PATIENTS

Twenty patients selected at random from the main group of 200 patients were interviewed by one of us (M.M.). All of these patients showed a pattern of regular attendance; four had been classified by us as A patients, ten as B patients and six as C patients. The purpose of the interview was explained to the patients during one of their regularly scheduled visits to the o.p.d. The format of the interview was left relatively unstructured; however, we paid particular attention to those aspects of the interview which appeared to be more directly related to the scope of our study. As a rule, the patients were cooperative and declared themselves glad to show their gratitude for the assistance received by the hospital, in this way. Most of the patients, however, spoke profusely about their complaints and about half of them tried to utilize the interview situation to elaborate on symptoms which, as one patient expressed, "the other doctors pay no attention to," or by asking for further tests or consultations. One striking observation was that none of the patients ever mentioned spontaneously the name of the treating physician; they all seemed to have a relationship of attachment and dependence on the hospital rather than their treating physician. This finding has been emphasized also by A. Levine in a psychological study of a similar group of chronic patients (17).

Some patients who had received psychiatric attention, either in the form of consultation or a brief period of attendance at the psychiatric clinic, appeared to be resentful about it, felt that this had been unnecessary and that it actually stemmed from the fact that their treating physicians had not really understood their problem.

Some typical cases are briefly described below:

CASE 1. Chart #33-11094. A 62 year old housewife has been attending the o.p.d. without interruption since 1932. She visited 13 different clinics, averaging about 17 appointments per year. She received the following diagnoses: bronchial asthma, cholelithiasis, cervical erosion, pruritus vulvae, menopausal syndrome, mild osteoarthritis of the spine and neurasthenia. At present, she regularly attends the eye clinic for treatment of cataracts and the arthritis clinic for low-back pain. Twenty-two laboratory tests were performed, 18 of which proved to be negative. Of the five different consultants to whom she was referred, only the psychiatric

consultant elicited positive findings and made a diagnosis of conversion hysteria and anxiety state. The patient attended the psychiatric o.p.d. a few times only and states that this had been a mistake on the part of the doctors because "they did not believe my pains were real." During the interview, the patient appeared glad that another doctor was interested and she talked profusely about her many complaints. She stressed her low-back pain much more than she did the far more serious eye condition. She did not remember any names of physicians and she called the hospital "a second home for me." During the interview other disturbances in the social and family life became apparent; her affect and her thoughts revolved mainly around her somatic complaints. The diagnosis was of character neurosis of long duration with marked hysterical and anxiety features. She appeared to be a passive and dependent personality.

CASE 2. Chart #33-10364. The patient is a 47 year old unmarried man who has been attending the o.p.d. since 1932, with an average of 32 appointments per year. He had visited six different clinics. Nine routine laboratory tests were performed, all of which proved to be negative. He received seven consultations, and only two confirmed very minor positive findings (tonsillitis and seborrhea). The psychiatric consultant made a diagnosis of "ambulatory schizophrenia" and since 1934 the patient has been attending the psychiatric o.p.d. It is of interest to note that since the patient began attending the psychiatric o.p.d. he stopped visiting the medical clinic, which he most frequently attended up to that time. During a four year interval, after he had been temporarily discharged from the psychiatric o.p.d., his visits to the medical clinic increased remarkably. At the time of admission, the patient was complaining of precordial pain and palpitations. He suffered from anxiety attacks and following the death of his mother he had an acute hallucinatory episode. His present complaints are vague and he is not certain that there has been much improvement in his condition. It seems, however, that his anxiety attacks occur less frequently. This patient tried to utilize the interview to obtain individual rather than group therapy, which he is receiving at the present time. The psychiatric history and the mental status offer no doubt as to a final diagnosis of schizophrenia. The patient leads a very withdrawn life, is unemployed and is supported by the Welfare Department. His thinking was concrete and his affect shallow and inappropriate.

CASE 3. Chart #33-11755. The patient is a 64 year old widow who has been attending the o.p.d. since 1932. She has visited six different clinics averaging about 11 appointments per year. She was seen in consultation by an E.N.T. specialist because of epistaxis and by an endocrinologist who confirmed a diagnosis of menopausal syndrome. Her first visit to the o.p.d. was clearly determined by symptoms of depression and anxiety following the death of her mother. During the course of her attendance six different clinical entities were diagnosed and a diagnosis of psychoneurosis was made in the medical clinic. She was not referred for psychiatric consultation. At the present time, the patient attends the diabetic clinic, although she has had neither clinical nor laboratory evidence of diabetes since 1955. During the interview the patient minimized her past emotional difficulties, stating that they were simply the transitory results of unfortunate events in her life. She feels greatly improved and is only occasionally depressed for short periods of time. The patient links her improvement with the disappearance of gynecological symptoms (cystocele, uterine prolapse, cervical erosion, and menopausal syndrome). We were able to confirm mainly from the anamnesis, a diagnosis of psychoneurotic reaction, although at the present time, the patient appears well adjusted to her environment, is active in community affairs and is relatively symptom free.

#### DISCUSSION

The practical implication of this study lies in the fact that 147 (73.5%) of a group of 200 patients attending a general o.p.d. for ten years or longer have a psychiatric syndrome able to be diagnosed. It appears that the number of patients with psychiatric illness increases in direct proportion with the length of the attendance. In fact, a comparison between the main group of patients and a control group of fifty patients attending the general o.p.d. for two years only



shows that in the latter there were 14 (28%) patients with a psychiatric diagnosis.

In regard to the problem of whether a relationship exists between the pattern of attendance and the presence of a psychiatric illness, our findings show that in the group of 168 patients with continuous attendance there were 132 patients (78.8%) who had psychiatric manifestations, thus indicating a positive correlation between regular attendance and the presence of psychiatric illness. However, even among the 32 patients with discontinuous attendance, there were as many as 15 (47.8%) patients with psychiatric disturbances. The psychiatric factor *per se* cannot, therefore, be held solely responsible for a pattern of continuous attendance. On the basis of our study other elements seem important in this respect and will have to be appraised as contributory to the pattern of attendance over a long period of time. These elements are briefly outlined here:

- A. The personality structure and attitude of the patient;
- B. The severity of the psychiatric manifestation;
- C. The concomitant presence of one or more physical illnesses and their severity;
- D. The attitude of the treating physician;
- E. Environmental and social factors.

Although our survey is primarily concerned with the non-psychiatric O.P.D. services, the following remarks by C. P. Blacker seem pertinent. In his study of psychiatric O.P.D. services in England he states that "many clinics easily slip into the habit of accumulating a massive and unwieldy attendance of chronic patients who haunt the O.P.D. year in and year out, reporting fluctuations in their condition but making no essential progress. They are frequently sustained by habit and a superstitious faith in the quality of the medicine which the hospital provides. Such chronic patients unduly magnify the number of return attendances, and it is frequently found that they have lapsed into this dependency because a definite line was, for one reason or another, not taken when they first attended the clinic." (18).

Those of our findings which relate to the utilization of the O.P.D. facilities are of particular importance from the point of view of medical care and administration. We were able to demonstrate that the patient with a psychiatric condition (a) tends to make more visits to the O.P.D., (b) attends a greater number of different clinics, (c) is referred more often for consultations, and (d) shows a much higher percentage of negative results in the laboratory reports than the patient whose primary diagnosis is a medical one.

The survey we conducted, using the clinic records as the main source of material, has permitted us to arrive at a comprehensive view of the unfolding of somatic and psychiatric symptoms in the same patient. This method, although not a substitute for a direct and prolonged observation of patients, offers in our view, a concrete contribution to meet the often stressed need for a comprehensive approach to the problems of the patient. It is pertinent to remark that we derived from our study a substantiated impression that the two sets of symptoms, somatic and psychic, were often considered and treated as isolated and separate



manifestations rather than as interrelated phenomena. A practical suggestion would stem from these considerations: In view of the great number of patients presenting the marked tendency we observed to frequent the o.p.d. and in view of the limited amount of time that the treating physician has available, it would seem doubtful that a simple increase in the awareness, on the part of the physicians of the problems presented by these patients is the only answer. In addition, in the present setup the need for further research in this field could not be easily satisfied. It might be worthwhile to consider the establishment of a special clinic center where this category of patient could be treated and studied by a team of psychiatrists and other specialists.

We shall mention only, with regard to further investigation, our observation that in both groups of patients with continuous and with discontinuous attendance there was a high percentage of psychoneuroses. Whether the different patterns of attendance actually do correspond to a different course of the condition could not be assessed in this study. However, a study of the possible factors influencing the manifestations and the course of diagnostically similar conditions would contribute significantly to psychiatric knowledge (19). Another finding of interest is that there are patients who tend to develop multiple illnesses. Usually these patients have emotional difficulties; in this sense our finding is in keeping with the already mentioned observation of Hinkle and Wolff (13). However, we also observed that other patients whose primary diagnosis was of a psychiatric disorder, exhibit multiple somatic "complaints" which are not able to be diagnosed as diseases. We can only speculate, generally, on the different roles played by constitutional and environmental factors in these various groups of patients. In conclusion, it seems important to stress the practical and heuristic value of a study such as the present one.

#### SUMMARY

A survey of 200 clinic records of patients attending the general o.p.d. of The Mount Sinai Hospital of New York for ten years or longer revealed the presence of psychiatric disorders able to be diagnosed in 73.5 per cent of the cases. Further analysis of the data showed that patients with a pattern of continuous attendance had an even higher incidence of psychiatric illness (78.8%) when compared with patients who had attended the o.p.d. at irregular intervals;

B. The impact of these patients with long-term attendance on the general function of the o.p.d. was studied in relation to the utilization of various facilities (number of clinics visited, number of appointments made, use of the laboratory, and the number of consultations undertaken). There was a highly significant difference in this respect between patients with a psychiatric illness and patients whose primary condition was a medical one;

C. Two main pathological profiles were found among the patients with psychiatric symptoms. (1) Some patients (Subgroup A) developed several somatic complaints most of which were not substantiated by clinical or laboratory findings and relatively few clinical entities were diagnosed. The primary diagnosis in these patients was of psychiatric disorder. (2) On the other hand, the largest

single patient group in our sample (Subgroup B), developed signs and symptoms of well recognized diagnostic entities; diagnoses were made in a significantly higher number in this group when compared with the other groups of patients constituting our sample;

D. Age and sex differences were found to be related both to the patterns of attendance and the presence of psychiatric disorders;

E. The ambivalent attitude of the o.p.d. physicians and the difficult problems of management that these chronic patients pose are stressed;

F. The implications of our findings in relation to better medical care and clinical research are discussed.

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# DIABETIC RETINOPATHY AND RETINAL MICROANEURYSMS

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In 1877, 26 years after Helmholtz (1) described the first ophthalmoscope, the lesion most characteristic of diabetic retinopathy, the microaneurysm, was clearly described for the first time by Mac Kenzie (2) and Nettleship (3). Their descriptions, however, were ignored until 1943 when Ballantyne and Lowenstein rediscovered retinal microaneurysms and studied them in greater detail in patients with diabetic retinopathy (4). Microaneurysms are now known to occur also in retinal vein occlusion (5, 6), malignant hypertension (7), arteriosclerosis (8), thrombotic and other glaucomas, chorioretinitis (9), sickle-cell disease (10), Cushing's syndrome (11), pernicious anemia, retinoblastoma, and Eales' and Coats' Disease (12). In almost thirty per cent of supposedly normal retinas examined pathologically, Ashton found microaneurysms, about one-half of them being located in the extreme periphery of the retina (9).

Retinopathy is believed by some to be the most common vascular lesion in patients with diabetes mellitus, and its incidence is rising as the life span of diabetics increases (13). This finding is being reported more frequently in juvenile diabetics; Larsson *et al.*, in 1952, reported retinopathy in 24 of 33 juvenile diabetics whose primary disease was present for 15 or more years (14). Ashton, by combining the results of many series, has shown that the tendency to develop retinopathy correlates best with the duration of diabetes, there being a striking increase in the incidence of retinopathy after 10 to 15 years (15). In studies quoted by Ashton the incidence varied from 60 to 93 per cent after 15 to 20 years of diabetes mellitus. The fact that Joslin has reported cases free of retinopathy after 25 years demonstrates that this is not an inevitable complication of diabetes (16). While the appearance of retinopathy may occur very early in the disease, even in some cases prior to the appearance of clinical symptoms of diabetes, Hardin *et al.* found that it takes an average of thirteen years to develop retinopathy (17). Whether sex, severity of the diabetic state and degree of control of the disease can be correlated with retinopathy is greatly disputed.

It should be emphasized that many of the early changes of diabetic retinopathy are asymptomatic and that diminished visual acuity occurs only with macular involvement, severe vitreous hemorrhage, retinitis proliferans or retinal detachment (15, 18, 19). These are the end results of a complicated and often progressive process which is usually bilateral, although the extent of involvement may vary in the two eyes.

The earliest visible manifestation of diabetic retinopathy is the appearance, in the central area of the fundus, of microaneurysms which are usually 20 to 30 microns in diameter (19) (the limit of ophthalmoscopic visibility) al-

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though they may be three times as large (9). These microaneurysms are seen microscopically to be round or oval shaped swellings in the inner nuclear layer of the retina on the venous side of the capillary network that joins the deep and superficial capillary plexuses (20). The microaneurysms are seen to be well demarcated and have PAS-positive basement membranes that may be either thickened or split and disintegrating (9). Ballantyne and Lowenstein stated that the earliest microscopic change in diabetic retinopathy is the appearance in the capillary endothelial wall of lipoid material, producing localized weakening of the capillary wall, predisposing to aneurysm formation (14). Some of the microaneurysms arise as minute buds or diverticulae in such an injured area, and from this stage they gradually enlarge. Ashton (9) has discovered that they also originate frequently from loops in vessels which become varicose; exudate composed of mucopolysaccharides (20) and lipids (19) then passes through the vessel walls causing adherence of adjacent vascular surfaces with resultant indentations (which later may disappear) opposite the microaneurysms.

Though microaneurysms may not change their gross appearance for many months, exudates rich in lipoid and PAS-positive material (presumably mucopolysaccharide) ooze through and may become incorporated into their walls to form a laminated "cap" and may even produce obliteration of the aneurysm cavity leaving a round, hyaline nodule. Some of this exudate passes into the outer molecular layer of the retina to form well defined waxy exudates (15) which may form rings or crescents around microaneurysms (21). The exact physical and chemical nature of the waxy exudates of diabetic retinopathy is still unknown. Scarlet red staining reveals that they are composed in part of fat and PAS staining indicates that they probably contain mucopolysaccharides as well (19). The exudates occupying large cystic spaces commonly appear as a central mass of either albuminous or hyaline material surrounded by a zone of fatty substance. Those exudates which are seen bordering retinal vessels are composed of fatty granular cells. Retinal exudates have a tendency to coalesce and form the typical confluent waxy patches seen in moderately advanced cases of diabetic retinopathy (19). Exudates occasionally resorb spontaneously.

Erythrocytes may escape from the circulation by rupture of a microaneurysm or by leakage through vessel walls damaged by fatty deposition to form irregular "blot" hemorrhages. Microaneurysms may be distinguished from hemorrhages because they have a sharp outline, seldom exceed 60 microns in size, often are only 20 to 30 microns in diameter and maintain their small size for a long period of time. So-called "blot" hemorrhages are larger, irregular in contour and may have a vague border. They vary more in size, may be located deeper than microaneurysms and have a tendency to be resorbed. Histologically, the hemorrhages lack the endothelial lining of microaneurysms and do not communicate with the capillaries (15, 19).

Ballantyne (19) and Friedenwald (22) are among the many authors who described further retinal vascular changes in diabetics consisting of alteration in the caliber of the retinal veins commencing several millimeters from the disc,



characterized by intermittent enlargement or beading, looping, kinking and the appearance of newly formed vessels. This process of neovascularization has been studied by Wise, who feels that microaneurysm formation is an arrested effort at new vessel formation which, if progressive, leads to fibroproliferative changes, vitreous hemorrhage and retinal detachment (12, 23). Wise, quoting his own work (12, 23), and that of Michaelson (24), has stated that neovascularization, either arrested as microaneurysm formation or progressive, is a response to retinal anoxia which is the stimulus for the production of a vasoformative substance termed "factor x". "Factor x" is believed to be absent in the normal, mature retina but appears following retinal capillary or venous obstruction. The anoxia produced by interference with retinal circulation presumably initiates the production of "factor x" and new blood vessels may then be formed which bypass the obstruction to supply the adjacent retina.

Michaelson pointed out that embryonal retinal capillaries develop by budding from pre-existing veins and tend to grow from the side of the vein farthest from an artery (24). He stated that this vascular growth occurred in response to some unknown factor ("factor x") arising in areas of relative retinal anoxia; when the new vessels satisfied the retinal oxygen requirement, "factor x" disappeared or ceased to exert a trophic effect. Michaelson believes that this embryonal capacity of capillaries and veins to proliferate in response to anoxia remains after birth in a dormant state. In attempting to describe the unknown factor, Michaelson characterized it in the following ways:

- A. It is present in the extravascular embryonal retinal tissue, thereby accounting for its effect on the side of the vein away from the artery;
- B. It is present in different concentrations in arterial and venous areas;
- C. Its action is primarily on the venous side of the retinal circulation;
- D. The extent of neovascularization, either abortive or progressive, is proportional to the concentration of the unknown factor (24).

Wise believes that venous obstruction, regardless of its pathogenesis, is the unifying element in stimulating production of "factor x" in the various retinopathies characterized by microaneurysm formation in response to anoxia (12). He states, "These lesions are not actual aneurysms but represent aborted attempts at neovascularization. Either a minimal retinal anoxic tissue stimulus is satisfied by their bulge toward the stimulating point and the coincident better oxygenation of this area, or new blood vessels growing from adjacent more strongly stimulated veins and capillaries reach the anoxic area first, satisfy the relative retinal anoxia present, and restore equilibrium and neovascular growth ceases, leaving these aborted neovascular buds in its wake." Klien and Olwin (25), Becker and Post (5) and many others have observed microaneurysm formation following retinal venous obstruction. Ballantyne (19) demonstrated venous and capillary obstruction in diabetics with neovascular changes in their fundi; Ditzel and White (26) noted similar changes. Retinal neovascularization has been attributed to venous obstruction in cases of sarcoid, polycythemia and malaria, but has been studied more fully in sickle-cell disease (12).

Our knowledge of the pathophysiology of sickle-cell disease and its ocular



complications further supports the concept of Wise. Edington and Sarkies in 1952, described two cases of sickle-cell disease with retinal microaneurysms situated on or adjacent to peripheral venules (27). Hannon, in 1956, reported venous occlusions and neovascular changes in the fundi of patients with sickle-cell hemoglobin C disease (28). In 1957, Goodman *et al.* described five patients with sickle-cell disease, four with sickle-cell hemoglobin C, and one with probable sickle-cell hemoglobin D (10). These investigators found abundant evidence of retinal and preretinal neovascularization arising from the venous circulation in their subjects. They also noted that microaneurysms and vascular networks developed on the arteriolar as well as the venous side of the circulation. Ashton noted similar changes on the arterial side of the retinal vascular bed in long-standing diabetics (8).

Wise quotes other observations compatible with his hypothesis (12). The fact that aneurysms may develop from one or both sides of a capillary is explained by stating that in the former instance the neovascular stimulus lies to the side of the capillary bearing the aneurysm, while in the latter, the capillary lies within the anoxic area, the stimulus being applied to both endothelial walls with resultant beading of the vessel (12). That microaneurysms are often seen in the absence of capillary wall damage and may be lacking in some areas of obvious capillary wall disease suggests that a factor other than local endothelial pathology initiates their appearance. The observation that microaneurysms are seen in a variety of conditions associated with retinal venous stasis and anoxia further supports Wise's theory.

Ashton has recently criticized this concept, stating that the retinal capillary endothelium is the same as that found in other areas of the body, but that microaneurysms are probably unique to the retina. He also noted that animal experiments producing retinal neovascularization have not been successful in creating microaneurysms (20). Thirdly, Ashton stated retinal microaneurysms often exist in the absence of other evidence of neovascularization and that the converse is also true. These objections, though quite pertinent, may be overcome by close application of the work of Michaelson and Wise to each of Ashton's statements:

A. First, though there is no evidence that retinal capillary endothelium differs from that found elsewhere, the essential feature of the retinal neovascularization process is thought to be the awakening, via an anoxic stimulus, of a quiescent, embryonal factor, unique as known to the retina; the capillary wall is thought to respond to, not initiate, the stimulus to proliferate.

B. Second, Wise (12) has stated that the failure of Ashton's experiments in retrolental fibroplasia (29) to produce microaneurysms may be due to the marked arterial and venous obliteration produced, which may act as a great neovascularizing stimulus causing all neovascular buds to form new vessels. Retinal microaneurysms, according to Wise, are aborted attempts at neovascularization, their progression to new vessel formation being limited if they can satisfy local oxygen demands. In experimental retrolental fibroplasia the anoxic stimulus is presumably greater than can be met by microaneurysm formation.

C. Ashton's third objection, that microaneurysms may be noted funduscopically in patients without other evidence of neovascularization, is invalid if one accepts Michaelson's contention that the extent of new vessel formation is proportional to the degree of anoxia, that is, the amount of "factor x" liberated. The equilibrium between retinal oxygen demand and supply may be restored only by microaneurysm formation in some clinical conditions.

However, I believe that there are grounds for not fully accepting the conclusions reached by Wise. No statement has been made about the nature of "factor x". The substance has not been isolated and, therefore, has not been proven experimentally to produce neovascularization. Though microaneurysms have been identified in several conditions characterized to varying degrees by retinal anoxia, neovascularization has not as yet been reported to occur in the majority of clinically anoxic states. The theory is a useful one as it offers explanations for many observable phenomena, but, because of current inability to demonstrate the actual presence of "factor x" and lack of confirmation of the basic role of retinal anoxia in neovascularization, judgment must be withheld concerning its validity.

Ashton *et al.* proposed in 1957, that disturbances in retinal fluid balance may be of importance in the pathogenesis of diabetic retinopathy (29). By injecting such enzyme-inhibiting substances as sodium fluoride and sodium iodoacetate into kitten eyes, they were able to interfere with glycolysis and observe changes suggestive of swelling in immature retinas. Their results were interpreted as possibly being due to osmotic imbibition of fluid by the retina when glycolysis ceased, resulting in elevation of intraretinal pressure followed by compression and obliteration of the vessels. These vascular changes were reversible by injecting hypertonic solutions into the vitreous, but not by similar injection of isotonic solutions. It was also found that retinal detachment protected against vaso-obliteration in these experiments. Graymore subsequently showed in *in vitro* experiments using the kitten and rat retina that sodium fluoride inhibition promotes the passage of water into the retina (30, 31).

Ashton believes that in central artery occlusion, malignant hypertension and arteriosclerosis, anoxia promotes the formation of catalytic substances, which produce an osmotic imbibition of fluid into the retina with ensuing obliteration of capillaries by extrinsic pressure (20). He further states that microaneurysms have been found associated with avascular areas in these conditions. He proposes that elevated intraretinal pressure, which is capable of causing stagnation of capillary flow, anoxia, capillary microaneurysms and new vessel formation, may be the fundamental pathological process in the various retinopathies characterized by microaneurysm formation and neovascularization. Ashton concludes, "In the metabolic defect of diabetes the retina, being so particularly dependent on the breakdown of glucose as an energy source and having a higher glycolytic rate than almost any other tissue, is subject to a chronic metabolic disturbance leading gradually to failure of osmoregulation with the imbibition of water and increase in retinal turgescence. The resulting rise in tissue tension impedes the capillary circulation, stagnation and anoxia result, and micro-

aneurysms form. The arteriolar obliteration may be the late results of this process, but the process is more complicated since arteriosclerosis and hypertension have also to be taken into consideration." That microaneurysm formation can be attributed to elevated retinal pressure is an attractive hypothesis applicable to many conditions characterized ophthalmoscopically by these lesions, but further proof and clinical confirmation of this phenomenon are lacking at this time.

A great deal of interest has been aroused in recent years by demonstration of various biochemical aberrations in diabetics and by attempts to correlate these findings with complications of the disease. I shall review very briefly some of the controversy in certain areas of research.

Histochemical studies of the retinal and renal complications implied to some investigators that elevation of serum mucopolysaccharide might be responsible for these changes. Berkman *et al.* (32) demonstrated, and Ejarque *et al.* (33) confirmed a progressive rise in the level of serum protein-bound carbohydrate with the onset of vascular complications of diabetes. It is currently believed that elevation of serum protein-bound carbohydrate is a nonspecific reaction, probably not related etiologically to diabetic vascular complications and represents a probable manifestation of tissue breakdown in these patients (15).

It has been postulated that elevated serum lipoprotein levels might be implicated in the retinal vascular complications of diabetes by production of atheromata, injury to capillary walls and by slowing the rate of vascular flow in the smaller vessels (20). In a large series of diabetics investigated by Gofman *et al.* there was an elevation of molecules of the  $S_f$  10 to 20 class, especially in those with vascular complications (34). Keiding was also able to relate this class of lipoprotein to diabetic retinopathy (35). It should be noted, however, that Gofman found this lipoprotein fraction to be elevated in arteriosclerosis, nephrosis and myxedema in the absence of retinal changes of diabetes (36, 37). Lewis and Page reported similar elevations in cases of malignant hypertension treated with pyrogens (38). Though alterations in lipid metabolism are nonspecific, they may form the basis for rational therapeutic endeavors in the management of diabetic retinopathy. Van Eck has recently reported marked clearing of retinal exudates in diabetics who followed a 20 Gm fat diet; further trials with this regimen may confirm its efficacy and perhaps cast new light on the relations of lipid and lipoprotein metabolism to diabetic retinopathy (39).

Becker (40, 41) and Friedenwald (42) have proposed that adrenal cortical hyperfunction may be responsible for diabetic retinopathy and nephropathy. Becker reported the appearance of microaneurysms after intravenous ACTH therapy for sarcoidosis and demonstrated, after administration of ACTH, the prompt eosinopenic response of diabetics with retinopathy compared to diabetics without retinopathy who manifested no eosinopenia after ACTH. Becker also demonstrated pathologically that the weights of adrenals of patients with glomerulosclerosis were 24 per cent greater than the control group without renal disease. Eighty-six per cent of the adrenals from cases of glomerulosclerosis

manifested vacuolization of the zona fasciculata compared to an incidence of 12 per cent in the control group. Russi, Blumenthal and Gray state that adenomas of the adrenal cortex are more common in diabetics than nondiabetics (43). It has been reported that diabetic patients with retinopathy excrete excessive amounts of free oxysteroids in their urine (44) while diabetics free of complications excrete normal amounts (45). Whether these observations can be implicated in the etiology of diabetic retinal and renal lesions, or merely reflect the conditions themselves is unknown.

Lawrence and others have reported cases of diabetic retinopathy occurring during pregnancy with postpartum remission (46). Dolger, however, pointed out that retinopathy is frequently improved by pregnancy and stated that he could recall no diabetic patient who developed retinopathy while taking cortisone (47). The report by Mc Cullagh in 1956 of 21 cases of Cushing's syndrome, only three of which demonstrated retinopathy, argues against adrenal hyperfunction as the sole cause of funduscopic changes in diabetics (11). However, Poulsen reported the disappearance of diabetic retinopathy in a case of Simmonds' disease (48). Many reports of hypophysectomy for diabetic retinopathy have recently appeared with some improvement generally noted in visual acuity and/or funduscopic findings (49 to 52). Malins had little success with bilateral adrenalectomy in six diabetic patients (53).

Becker (64) and Friedenwald (42) proposed that vitamin B<sup>12</sup> deficiency induced by diabetes and exacerbated by adrenal hyperfunction might be one of the metabolic factors initiating production of the vascular complications. Friedenwald noted, however, that vitamin B<sup>12</sup> therapy in diabetic retinopathy was of little value, and Becker recognized that diabetics do not develop pernicious anemia as often as might be expected if vitamin B<sup>12</sup> deficiency were present in these cases (41). Theoretical, as well as clinical and therapeutic data, fail to support this contention.

In conclusion, it may be stated that the retinal microaneurysm is a feature of several diseases, each of which may be characterized to some extent by retinal anoxia (though they have not been reported to occur in many conditions in which anoxia is a prominent feature). Microaneurysms may represent physiologic efforts to restore retinal oxygenation, although the role of osmotic tension, recently publicized, may be a major factor in their pathogenesis. The relation of serum protein-bound carbohydrate, lipids and lipoproteins and adrenal hyperfunction to microaneurysms is unclear at this time.

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# CARCINOMA OF THE BREAST ASSOCIATED WITH PREGNANCY

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The appearance of a mammary tumor during pregnancy or the ensuing puerperium raises many questions which intimately involve the patient, her family, the physician, and the surgeon. It is a rare patient today who is not cognizant of the possible meaning of a breast tumor.

## INCIDENCE

In this country breast cancer is responsible for almost 18,000 deaths annually (1, 2). This is nearly 20 per cent of the deaths due to cancer among white females and nearly 17 per cent among non-white females.

The coincidence of carcinoma of the breast and pregnancy or lactation is rare. White collected the reports of 22 experienced authors with a total of 25,159 cases of breast cancer (3). Of these, 737 cases, or 2.9 per cent, were either pregnant or in the puerperium at some time during the course of the disease. He also reviewed the world literature on this subject and up to 1950 could find only 920 reported cases. In 1955 he noted the total number of cases to be 1375 (4). In the series of cases of breast cancer at the Mayo Clinic, Harrington found 92 pregnant women of the 4,628 patients treated for breast carcinoma (5). Finn reported on 62,561 patients observed at The New York Lying-In Hospital from 1932 to 1950 in whom there were only 46 cases of associated breast cancer (6). Overall, there is a reported incidence of three breast carcinomas per 10,000 pregnancies.

## PROGNOSIS

The combination of carcinoma of the breast and pregnancy or lactation is a virulent one; the survival rates are notoriously poor. Cheek reported a 5.3 per cent five year survival rate (7); Harrington, a 5.7 per cent five year survival rate (5). The prognosis is so poor that some surgeons have called the combination hopeless. Haagensen and Stout reviewed 29 cases of breast carcinoma associated with pregnancy or lactation (8). Of these, three survived five years, and two of these died shortly thereafter of recurrences. They concluded from their study that breast cancer occurring during pregnancy or in the puerperium was inoperable (9). This combination was later removed from their criteria of inoperability, but they commented on the persistently poor results obtained.

Further evidence of the high degree of malignancy of this combination is the relatively short duration of the disease. The majority of reports reveal an average of 32 to 48 months between the onset of the disease and death.

The highest incidence of breast cancer occurs in the 40 to 50 year age group. In the cases associated with pregnancy or lactation the average age is between 32 and 34. Carcinoma of the breast is a rarity in women under thirty, and under

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the age of 25 a curiosity. Less than two per cent of the patients with breast cancer reported from the Presbyterian Hospital were under the age of thirty, and only four were under 25 (10). Reviewing these data, one should be more suspicious of a mammary tumor in pregnancy or in lactation in a woman over the age of thirty than in one who is younger.

A tumor of the breast should lend itself to early diagnosis by the nature of its location. However, self-examination, important in the discovery of cancer of the breast, is not as simple during pregnancy or lactation, when there is physiological engorgement of the breast. The duration of symptoms in these patients averages over one year. This is about four months longer than in patients with breast carcinoma uncomplicated by pregnancy or lactation (11). The delay in seeking medical attention lies both with the patient and with the doctor who feels that the breast tumor is either an abscess or a benign tumor. A parallel study was performed by Westberg who studied the duration of symptoms in women with breast cancer associated with pregnancy and in those uncomplicated by pregnancy (12). The average woman reported her tumor to the physician two months later if she was pregnant or nursing than if she were not. The doctor after noting the mass, delayed an average of one month longer in treatment of a patient who was pregnant or nursing than in one without these complications.

#### ASSOCIATED PROBLEMS

In 1953 Cheek published a survey in which he submitted a list of five questions related to carcinoma of the breast associated with pregnancy or the puerperium, to 55 of the world's leading authorities on the subject (7). The first question was: "How many cases of carcinoma of the breast developing during pregnancy have you seen? In how many was a five year cure obtained?" A total of 151 cases was obtained with only 8 five year cures observed, at a 5.3 per cent cure rate. The second question was: "Should carcinoma of the breast developing during pregnancy be considered inoperable?" None of those who replied thought that pregnancy alone was an indication of inoperability. The third question was: "In the premenopausal age, does pregnancy following a previous radical mastectomy increase the chances of development of carcinoma in the remaining breast?" Most thought that a subsequent pregnancy did not play any role in the development of cancer in the remaining breast. On the other hand, Trout collected 15 cases in which pregnancy had occurred after radical mastectomy and of these carcinoma had developed in the remaining breast in 13 (13). None had survived five years. The fourth question was: "Should pregnancy be terminated in a patient in whom carcinoma of the breast develops in the first trimester; in the second trimester; in the third trimester? Would you expect the five year survival rate to be increased by the termination of the pregnancy?" More than half of those who replied thought that pregnancy should be terminated in the first trimester as well as in the second trimester. Should it occur during the third trimester, most felt that an attempt to obtain a viable child should be made. About one-third indicated that there was no reason to terminate the

pregnancy. Hochman feels that interruption of pregnancy has no influence on the course of the disease (14). White studied the relationship of the five year survival rates to the trimester of pregnancy in which the cancer of the breast developed, and concluded that the poorer results that he discovered in the second and third trimesters suggested that there was some tendency to treat less promptly or adequately than in early pregnancy (15). Adair believes that interruption of the pregnancy would benefit these patients (16). The fifth question was: "Should sterilization or tubal ligation be done following radical mastectomy in the premenopausal woman to prevent further pregnancies?" Half of those who replied thought that neither of these procedures need be done. One-third thought that one procedure or the other should be performed. Most indicated that subsequent pregnancies should be avoided because of the possibility of reactivating residual tumor cells, and that contraceptive measures be employed to avoid further pregnancies.

In 1952 a department of obstetrics was inaugurated at The Mount Sinai Hospital to complement a functioning gynecological service. Of the 31,671 admissions to the service during the period from 1953 to 1959, six patients were observed for pregnancy who had previously undergone radical mastectomy for carcinoma of the breast. The onset of pregnancy varied among these patients from two months to four and one-half years following surgery. Three of these patients were treated by therapeutic abortion in the first trimester. A fourth patient was treated by therapeutic abortion during the second trimester. The fifth patient was a forty year old female who was three months pregnant and fifteen months post radical mastectomy. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed combining a therapeutic abortion with removal of functioning ovaries. The sixth patient had a normal pregnancy and a spontaneous delivery 4½ years after a radical mastectomy for breast carcinoma. At present, she is pregnant again and is doing well six years after her breast surgery.

One death occurred in this series. This patient was a forty year old woman who became pregnant six months following a radical mastectomy for breast cancer. In her eight week of pregnancy she had a therapeutic abortion. She died of metastatic breast carcinoma 19 months following radical mastectomy and 11 months postabortion. The remaining five patients are at present alive and well with no evidence of recurrence of carcinoma of the breast.

#### TREATMENT

Treatment of mammary tumors must of necessity start with diagnosis. Some lesions of the breast are quite obvious to the trained observer. Lesions of infectious origin, such as lactation abscess, fall in this category. It is reasonable to attempt a cure with the proper antibiotic. However, if there is an underlying collection of pus, even in this antibiotic era, surgical drainage is often indicated. This procedure may serve not only to drain the pus, but also to obtain a biopsy of any suspicious area. A carcinoma may easily masquerade as an infected abscess.



Gershon-Cohen has illustrated that carefully taken roentgenograms often reveal the soft tissue details of some breast lesions (17 to 19). In many cases they have proved their preoperative diagnoses by correlating their findings with those of the pathologist. However, it is still an investigative technic and the microscopic examination of the biopsied specimen remains the prime diagnostic procedure.

The breast clinic at The Mount Sinai Hospital has initiated a program in which breast cancer is treated by combination treatment. Excisional biopsy is performed for diagnosis. If the frozen section is reported as malignant, a Halstead type radical mastectomy is performed, with complete excision en bloc of the breast, pectoralis major and minor muscles, and a complete axillary dissection. Prior to the definitive surgery, 15 mg of triethylenethiophosphoramide (Thio-TEPA®) is administered intravenously. At the end of the procedure the operative field is irrigated with 15 mg of Thio-TEPA dissolved in 250 cc of isotonic saline. In the postoperative period the patient is started immediately on a course of Thio-TEPA, 15 mg intramuscularly every other day for a total of five doses. Should a leucopenia develop, the treatment is interrupted and the patient is treated with antibiotics, and if necessary, blood transfusions. Thrombocytopenia (which responded to cortisone) has been reported in some patients.

A patient treated for carcinoma of the breast during the first trimester is advised to undergo a therapeutic abortion in addition to a radical mastectomy. If axillary metastases are present, the patient is advised to have a bilateral oophorectomy. Of course, this is a personal decision which must be thoroughly discussed and agreed upon by the patient, her husband and her physician.

A patient treated in the second trimester is advised to undergo a similar procedure as outlined above with the substitution of an abdominal hysterotomy as the technic of abortion.

The patient treated in the third trimester presents a different problem, with many individual answers. In many cases, the feasibility of obtaining a viable child, might take precedence over other considerations. Although radical mastectomy may be performed should breast biopsy be positive for carcinoma, delivery is deterred until a viable child may be obtained. However, after delivery oophorectomy is advised if axillary metastases were present.

The puerperium is generally considered to be a period of one year from the time of delivery. If a patient should develop a breast carcinoma during this period, the treatment outlined is advised. In addition to this treatment, chemotherapy is given to the patient as previously described. At present, the patient is rested for four to six weeks and a second course of TSPA (triethylenethiophosphoramide Thio-TEPA) is given to the patient consisting of 15 mg TSPA L.M. once weekly. This course consists of 75 mg TSPA and the patient is closely followed with complete blood counts and platelet counts. At the completion of the second course, the patient is started on a third course ten to twelve weeks afterwards. This course is similar to the second course. If the patient at any time develops a side reaction to the drug, the treatment is stopped and continued only after full recovery of the patient.



Radiotherapy is administered to the patient if the axillary nodes are positive for metastases. It is administered via the Cobalt-60 machine and it is given to the supraclavicular, parasternal and axillary regions, as well as to the operative area.

This combined form of treatment for the patient with breast cancer complicated or uncomplicated by pregnancy has been in effect for a short period, and it is too soon for evaluation. However, in the treatment of pregnant patients, there is great room for improvement in the five year survival statistics, and it is hoped that our results will reflect such improvement.

#### SUMMARY

A. The coincidence of carcinoma of the breast and pregnancy or lactation is rare. There is a reported incidence of three breast carcinomas per 10,000 pregnancies;

B. The survival rates in patients with the combination of breast cancer and pregnancy or lactation is very poor; in a large series the rate reported was five to six per cent. There is an average of 32 to 48 months between the onset of the disease and death;

C. The average age of these patients is 32 to 34. It is rare under the age of thirty;

D. The role of therapeutic abortion is discussed, as is that of castration;

E. The present outline of treatment instituted at The Mount Sinai Hospital is presented. This is an attempt to favorably affect the survival statistics associated with breast cancer.

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# *Clinico-Pathological Conference*

## HEPATOSPLENOMEGALY WITH ANEMIA, FEVER AND JAUNDICE

*Edited by*

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A 78 year old retired male cloth examiner was admitted to The Mount Sinai Hospital because of anorexia, weakness and constipation of six weeks duration; on examination before admission his physician had found jaundice, hepatomegaly and splenomegaly. He had been well until the onset of symptoms. When the constipation began, he took several doses of a saline cathartic which always produced several black bowel movements on the day the laxative was taken. Stools were otherwise normal in color. He had some heartburn relieved by antacids. In the six weeks prior to admission, he lost 12 to 15 pounds. After three weeks he noted light stools and dark red urine. No pain or pruritus was experienced. Two days before admission he developed some ankle edema and had three episodes of chills but no fever.

He was jaundiced for a few days at 15 years of age. He had had pneumonia at 48, a bilateral inguinal herniorrhaphy at 63, and intermittent black stools since 65. He had been taking no drugs other than antacids and aspirin. He had no exposure to jaundiced persons.

He appeared well nourished and in no distress. All vital signs were normal. He was slightly icteric with ruddiness of the upper trunk and face. A few vascular spiders were present on his chest. An enlarged left supraclavicular node, bilateral soft and non-tender axillary nodes up to 1.5 cm in diameter were felt. A few rales were heard in the right lung base. A soft systolic and early high pitched diastolic murmurs were heard. The liver extended 5 fingerbreadths below the right costal margin. It was firm, smooth and slightly tender. The spleen was felt 4 fingerbreadths below the left costal margin and was firm and non-tender. No ascites was present. Bilateral recurrent inguinal hernias were felt. The prostate was diffusely enlarged. Fairly severe pitting pedal and ankle edema were noted.

The urine specific gravity varied between 1.020 and 1.024. Traces of albumin were always present. The urine sugar was 4+ on admission and mild glycosuria was frequently found on repeated examinations. Bile and urobilinogen in dilutions of 1:160 were present in some specimens. Variable but small numbers of red cells, white cells and casts were present in all specimens. Stool guaiac reaction was 2+. BUN was 34 mg%, blood sugar 142 mg%, serum albumin 3.3 Gm%, globulin 2.3 Gm%, cholesterol 210 mg%, cholesterol esters 140 mg%, cephalin flocculation 2+, thymol turbidity 1.0 units, bromsulphalein retention 14%, glutaminoxalacetic transaminase 36 units, and prothrombin time 17.5 sec.

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with a control of 13 sec. Serum electrophoresis showed all components but alpha 1 globulin to be low. Serum mucoproteins were 123.5 mg%, and zinc sulfate turbidity was 3.2 units. The serum bilirubin was 1.2 mg% with 0.6 mg% glucuronide and one week later it rose to 2.0 mg% with 1.6 mg% glucuronide. The serum alkaline phosphatase was 24.6 King-Armstrong units initially and rose to 40.4 units. The sedimentation rate was 10 mm/hr. Hematologic data are outlined in Table I. Some hypochromasia, anisocytosis and a few spherocytes were noted on smear. Osmotic fragility of red cells was normal. Mechanical fragility was 8.4% with a control of 3.8%. Many blood cultures were all negative. *B. proteus* was grown

TABLE I  
*Hematologic Studies*

	Admission	1st week	2nd week
Hemoglobin (Gm%)	9.4	8.5	9.0
RBC (million/mm <sup>3</sup> )	—	3.92	3.57
WBC (per mm <sup>3</sup> )	4300	2300	2950
Segmented cells (%)	22	48	26
Band forms (%)	54	41	41
Lymphocytes (%)	23	4	32
Monocytes (%)	1	—	1
Atypical lymphocytes (%)	—	4	—
Reticuloeytes (%)	—	1.2	1.5
Platelets	—	198,000	144,000
MCV ( $\mu^3$ )	—	85	76
MCH (micro meg.)	—	37	24
MCHC%	—	32	31.5
Marrow			
Blasts (%)	0.5	Eosinophiles (%)	2.5
Promyelocytes (%)	2.5	Lymphocytes (%)	4.0
Myelocytes (%)	23.5	Plasma cells (%)	0.5
Eosinophilic myelocytes (%)	2.0	Reticulum cells (%)	1.0
Metamyelocytes (%)	18.0	Proerythroblasts (%)	1.5
Band forms (%)	9.5	Erythroblasts (%)	7.5
Segmented cells (%)	35.0	Normoblasts (%)	23.5

from the urine. The details of the bone marrow study are in Table I. The marrow was hypercellular with increased megakaryocytes. Erythropoiesis and granulopoiesis were active and no tumor cells were seen. A liver biopsy showed portal infiltration and fibrosis with destruction of the lobular periphery. Around the portal tracts atypical histiocytes surrounded and replaced necrotic liver cells. Chest x-ray revealed bilateral emphysema, blunting of the right cardiophrenic angle, a normal-sized heart and an elongated and tortuous aorta. An electrocardiogram was normal.

In the hospital he had almost daily chills and temperature spikes from a baseline of 100° up to 105°. He was given several blood transfusions, chloral hydrate, penicillin, streptomycin, Ilosone, Kantrex, Diamox, Diuril and Compazine. By

the end of the first week he became drowsy and his appetite decreased greatly. He also became quite short of breath. A flapping tremor and fetor hepaticus developed during the second week and at the end of the second week he became comatose and hypotensive. Nuchal rigidity was detected as well as bilateral basilar rales. The liver and spleen increased somewhat in size. The patient's temperature rose to 106.2° and after two days of coma he expired on the 15th hospital day.

*Dr. Martin C. Rosenthal:*\* This afternoon we have a case that has a wealth of information, probably most of it misleading, but we shall see where it takes us.

This was an elderly man who was a cloth examiner but it does not say if in his work he used any sort of benzine so we really know very little about whether he had any sort of long-standing chemical exposure.

His complaints were anorexia, weakness, and constipation. At this age such symptoms suggest the possibility of some type of neoplasm. He had intermittent black stools since he was 65. When the constipation began, we are told that he took a saline cathartic, and this cathartic always produced black bowel movements on the day that the laxative was taken. There are a number of vegetable cathartics which can do this, although we might consider the possibility that the black bowel movements represented melena. There was heartburn relieved by antacids, and recent weight loss of some severity. About three weeks before he was admitted he noticed the onset of some light stools and dark red urine without any pain or itching. This would perhaps suggest intermittent obstruction of the biliary tract.

The physical examination showed slight icterus, ruddiness of the upper trunk and face, vascular spiders, adenopathy, and a liver and spleen that were enlarged. The combination of ruddiness of the upper trunk and face and splenic and hepatic enlargement should suggest the possibility of some type of myeloid metaplasia. Frequently, patients who have polycythemia or one of its variants of polycythemia, when they become anemic, continue to display various vascular phenomena that we see in polycythemia. They will have a peculiar ruddiness of the face and display telangiectasia and even occasionally some spiders. Therefore, I think we should at least briefly mention the possibility of some form of myeloid metaplasia.

Naturally, the presence of vascular spiders and hepatic and splenic enlargement should raise the question of some type of long-standing cirrhosis. Cirrhotics occasionally, even when anemic, may display this peculiar ruddiness of the upper chest and face, sometimes even with a rather marked malar flush, due probably to the increase in the vascular changes associated with hyperestrogenemia.

There was a febrile course. With the systolic and diastolic murmurs and with splenic enlargement, the possibility of bacterial endocarditis is present, although later data make this most unlikely.

Severe pitting edema around the ankles, without evidence of congestive

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failure, was present. Malignant disease, especially intra-abdominal, may be associated with a rather peculiar type of edema, which stays confined to the ankles, and which does not regress particularly at night. We do not know whether this patient's edema cleared when he was put to bed.

He had some albuminuria, and, apparently for the first time, the patient was noted to have mild glycosuria with elevation of fasting blood sugar. A carcinoma of the pancreas could have caused splenic vein thrombosis leading to splenic enlargement; hepatic metastasis would account for the large liver. While this man had no back pain, this is not constant in carcinoma of the pancreas. And his initial complaints of anorexia, weakness and even constipation are consistent with malignancy. He had, at least on one examination, some blood in the stool, although it did not appear to be very much.

His serum albumin was slightly decreased but globulin was normal. Of importance was the fact that his cholesterol was normally esterified. Cephalin flocculation was 2+ and thymol turbidity was normal. His bromsulphalein retention, however, was abnormal. It is difficult to put these data, which are at variance, together. Some suggest no parenchymal involvement while others suggest definite hepatic impairment. His transaminase was normal, and prothrombin time abnormal. Again there was this peculiar dissociation of laboratory tests. Serum electrophoresis showed that all components were low; the most significant, of course, was the low gamma globulin. Once in a while, elderly people with hypogammaglobulinemia, splenic and hepatic enlargement are seen. These patients have recurrent infections. They usually are thought to have some type of lymphoma, although many of these patients at post mortem show nonspecific changes in the spleen and in the liver, and the exact basis for their hypogammaglobulinemia is not established. Associated with this syndrome is a hypersplenic picture, and this man had abundant evidence of hypersplenism. First, he has an anemia that was normochromic. He had a persistently low white count, and of the two platelet counts, one is normal and the other is at the lower limit of normal. This syndrome of low serum gamma globulin with an enlarged spleen and leukopenia and occasionally even cyclic leukopenia is now fairly well established, and this man possibly could represent such a picture. The only trouble with that is that in most of these patients there has been a fairly long-standing history of recurrent infections, such as one associates with the inherited type of hypogammaglobulinemia. So far as we can tell, this man had no previous infections. The serum mucoproteins were elevated which is very much in favor of some inflammatory or neoplastic process. At the same time we find that the zinc sulfate turbidity was low, which would confirm the electrophoretic prediction that the gamma globulin in this patient was low. The bilirubin showed that the icterus never was really very severe. The direct bilirubin was about half of the total bilirubin and at times somewhat higher. That suggests some liver disease, although it does not completely rule out hemolysis. In the urine we find that there were apparently traces of bile but the urobilinogen was considerably elevated to 1:160. The fact that the patient had increased urinary urobilinogen and also a slightly elevated serum bilirubin to-

gether with an enlarged spleen suggest that the basis for this icterus was a hypersplenic hemolytic anemia, mild and compensated, but nevertheless producing some anemia and some icterus. Indeed, on the smear, some spherocytes were noted, even though the osmotic fragility of the red cells was normal. Osmotic fragility of red cells as a rule mirrors what is seen on the smear. So far as the mechanical fragility goes, this was twice the normal, and again this might indicate and confirm the occasional spherocytes noticed on the smear. We are told that there were many negative blood cultures, examined no doubt because of the daily chills and temperature spikes as high as 105°. He was treated with a variety of antibiotics for a suspected generalized infection. The bone marrow was hypercellular with increased megakaryocytes, which simply indicates that this was a well functioning marrow, perhaps responding to the hypersplenism because of its cellularity with increased megakaryocytes. Certainly the fact that this type of bone marrow was found immediately rules out one of the possibilities that I mentioned, namely, myeloid metaplasia. The liver biopsy showed portal infiltration and fibrosis, and around these portal tracts there is mention made of atypical histiocytes which surrounded and replaced necrotic liver cells. That is somewhat difficult to interpret. The biopsy may indicate that the patient had some type of focal destruction of his hepatic cells, which elicited a phagocytic response, or else, taken even in a more grand fashion, it might indicate that there was actual infiltration in the portal region with a malignant type of cell. This patient deteriorated despite many measures taken. He became drowsy and there was a suggestion that he had hepatic decompensation; he developed a flapping tremor and fetor hepaticus. At the same time, he developed nuchal rigidity and bilateral basal rales. The latter suggests a terminal bronchopneumonia. Throughout his course, the liver and spleen increased somewhat in size. The patient died in a coma.

As I mentioned earlier, we have no lack of laboratory data or physical findings. Indeed, we have a plethora of them. I mentioned myeloid metaplasia as being fairly well ruled out because of the fact that the bone marrow was so cellular. I think a pancreatic neoplasm has to be considered but I just cannot imagine a spleen this large, and continuing to enlarge, associated with neoplasms of the pancreas. Occasionally we have seen patients with neoplasms who do indeed have associated splenomegaly, but the spleen is never so marked, and usually before it can enlarge further, the patient succumbs to his underlying disease. Is there a possibility that we are dealing with some infectious process? If so, the findings would indicate disseminated disease, such as miliary tuberculosis, or brucellosis. If such were present, there was certainly no response to what seems adequate antibiotic therapy. Furthermore, again, I cannot discard the fact that throughout the course the liver and spleen kept enlarging.

Lymphoma must be considered. This would explain the acquired hypogammaglobulinemia because in the older age group the commonest association of low gamma globulin is with lymphomas or with lymphatic leukemias. I would have to explain the hemolytic process on the basis of an enlarged spleen actively phagocytosing and removing blood cells. A small number of spherocytes can be

seen in association with that type of hypersplenism. I would also have to explain this peculiar liver picture. The liver biopsy with peculiar histiocytes and also the rising serum alkaline phosphatase, which went from 24 to 40 units, could indicate diffuse replacement or involvement of the liver, with lymphoma. What type of lymphoma could this be? We see a marked shift to the left in the white cell series, and usually that type of picture, with leukopenia, can be seen in Hodgkin's disease. One of the disturbing features about this diagnosis is the fact that the patient had a sedimentation rate of 10 mm/hr. That is very unusual, and the only way we could possibly explain or at least attempt to explain it is on the basis of lowered fibrinogen. If the patient had such diffuse involvement of his liver as to produce lowered fibrinogen, he would have a sedimentation rate that would be either normal or even subnormal. I do not think he had that severe liver disease; if he had I would expect more icterus and his lowered cholesterol. We might possibly explain that sedimentation rate on the basis of spherocytosis. The sedimentation rate to some extent does depend upon the interlocking of bi-concave discs, and when spheres are present, they will not form the regular long chains, which then rapidly sediment. This explanation would be more inviting if the patient had more than a few spherocytes, but apparently he did not, so that I am at a complete loss to explain the sedimentation rate.

In summary then, I would suspect that this patient had some type of diffuse lymphoma, possibly Hodgkin's disease, or some unusual type known in the foreign literature as reticuloendotheliosis. Sometimes it means Hodgkin's disease and sometimes it means a different type of lymphoma. I would think that he certainly had involvement of his liver and spleen, and I would not be surprised if he had rather extensive involvement of the abdominal lymph nodes, because the febrile course is seen usually with rather extensive abdominal involvement. I would also think that he had associated with this process hypogammaglobulinemia, a hemolytic process, and terminally a bronchopneumonia.

*Dr. Frederick G. Zak:*\* At the time of the autopsy, the body was icteric, and after opening the body cavities we found a rather extensive hemorrhagic bronchopneumonia in the left lower lobe and the right middle and right upper lobe, which was the immediate cause of his death. There was also a tracheobronchitis and a lesion in the left main bronchus, which was interpreted as a fungus infection. However, the main findings were that this man had a liver which weighed close to 2700 Gm and a large spleen which weighed 850 Gm, about six times the normal weight. In addition he had enlargement of the deeper lymph nodes, the mediastinal, para-aortic, lumbar and the iliac nodes all being enlarged, grayish and soft. There was no fibrosis, necrosis or hemorrhage in these nodes. The superficial lymph nodes hardly participated in this process, and, as you will remember, clinically they were described as only somewhat enlarged. In the bronchi there was an extensive suppurative inflammation. In the lumen filaments of a fungus were seen penetrating into the deeper layers.

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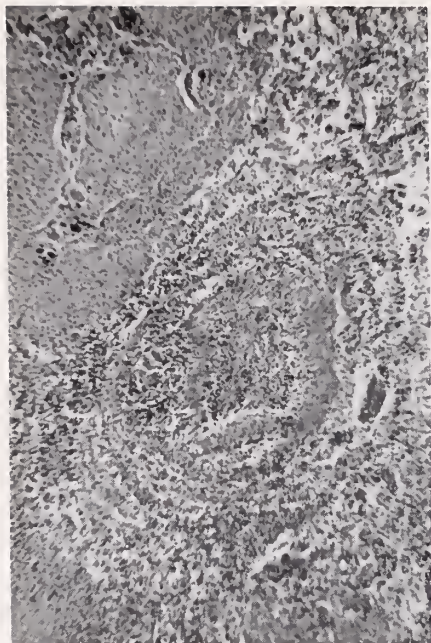


FIG. 1. Section of lung showing severe acute arteritis (H & E  $\times 63$ ).

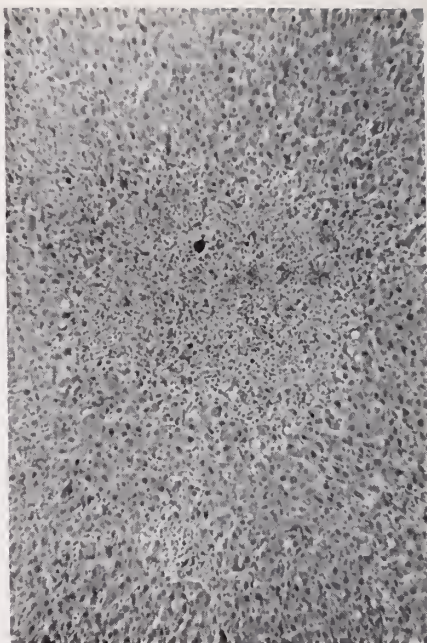


FIG. 2. Section of lung showing infiltration with histiocytes (H & E  $\times 63$ ).

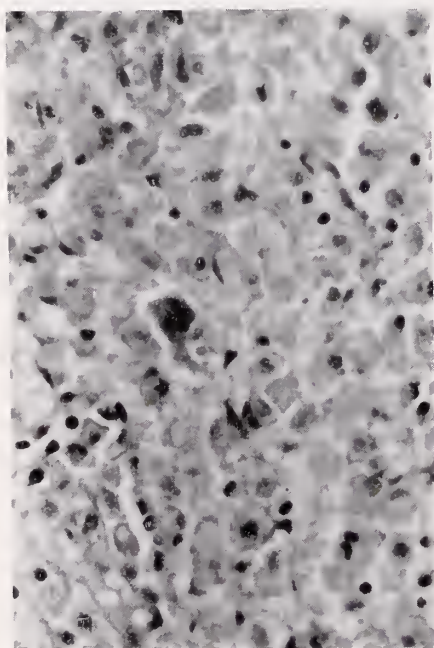


FIG. 3. Section of spleen showing giant cells and erythrophagocytosis (H & E  $\times 560$ ).

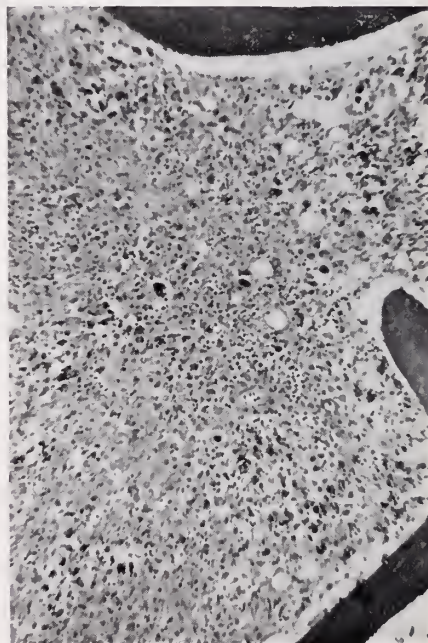


FIG. 4. Section of bone marrow showing extensive infiltration and giant cells (H & E  $\times 63$ ).

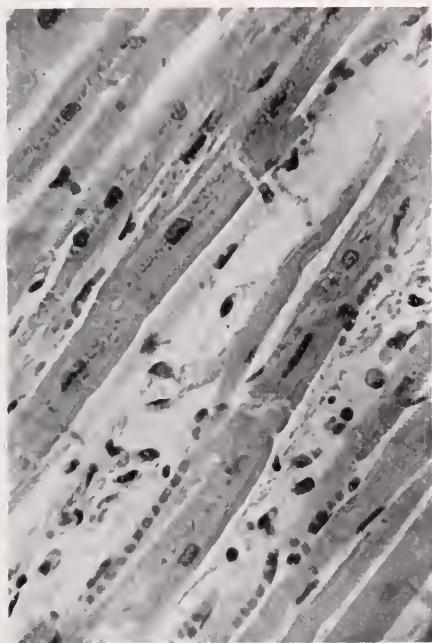


Fig. 5. Section of myocardium showing streak-like infiltration (H & E  $\times 320$ ).

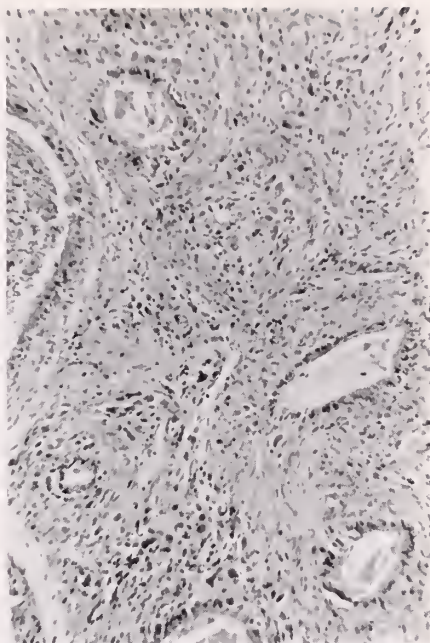


Fig. 6. Histiocytic infiltration of the epididymus (H & E  $\times 125$ ).

Purplish fungal filaments (PAS stain) were scattered in the pneumonic exudate, a terminal finding in a cachectic person regardless of therapy, nowadays seen more often in aggressively treated leukemias or carcinomas. Arteries in the area of pneumonia had become acutely inflamed (Fig. 1). However, this is not a systemic acute arteritis but a reaction to pneumonia. The man had guaiac positive stools, and we found an erosion near the pylorus of the stomach. The surface epithelium was missing, and there was a good deal of fibrin and acute inflammation in the wall.

A low power examination of the lymph nodes showed a total effacement of the normal lymph node architecture, which made it a malignant lymph node, type to be determined. At a somewhat higher magnification, a few scattered giant cells were seen, and, of course, you say, "Well, this is Hodgkin's disease." Cells meeting the criteria of Sternberg-Reed cells were present but cells of this type can occur in a variety of diseases. Although one would not make the diagnosis of Hodgkin's disease in their absence, their presence is not pathognomonic of Hodgkin's disease unless other features are also present. In lymphatics on the margin of the lymph nodes, there was an accumulation of large histiocyte cells which apparently had become mobilized and were now traveling through the lymphatics. The lymphocytes were greatly decreased in number and the entire node was replaced by sizable reticulum cells or macrophages. You will recall that Dr. Popper reported in the liver biopsy there were atypical histiocytes. The cells which traveled in the marginal sinus of the



lymph node stained a distinctly pinkish color with periodic acid Schiff (PAS) stain. Within the parenchyma of the liver, fairly sharply outlined areas were noted which were in the periphery of the lobe or in the portal space and were composed of atypical histiocytes only occasionally looking like Sternberg-Reed cells (Fig. 2). These infiltrates were extensive and since the liver weighed about a kilogram more than it should have, you can realize how much of the liver weight was caused by this extraneous tissue. Some of these cells apparently had been washed into the liver from the spleen and were not hepatic cells per se. Iron stains of the liver showed surprisingly little iron.

On first glance of the spleen, complete loss of the typical architecture was noted. The follicles could hardly be made out. In some areas almost every cell seen was a large histiocytic cell actively engaged in red cell destruction, and pale areas in the cytoplasm were hemolyzed red cells which they had engulfed (Fig. 3). As Dr. Rosenthal postulated, a massive erythrophagocytic activity on the part of these infiltrating cells was thus demonstrated. In the spleen larger cells, which may have been megakaryocytes, were occasionally seen. However, these cells were by no means common. They were scattered through the splenic pulp. An iron stain of the spleen showed a few deeply positive cells. The bulk of the erythrophagocytic histiocytes did not contain much iron. These histiocytic cells tended to round off. They lined the sinusoid of the spleen but they also became free and could thus be washed into the liver. The bone marrow at first glance was normal in some areas and abnormal in others. There were no fat cells in the abnormal area and this explains the fact that the marrow aspiration, apparently hitting normal marrow, missed the infiltrate which was best seen in the sections from the spine. Large pale cells formed extensive sheets of infiltration replacing normal marrow (Fig. 4). The fibrous stroma was not increased. In the pancreas, a focus of large histiocytic cells with peculiar finely granular cytoplasm was seen and also in the myocardium between muscle fibers the same cells were scattered in a streak-line fashion (Fig. 5). These infiltrations had a distribution which resembled that of leukemia, were deposits are found in many organs. A rather unsuspected lesion was in the epididymis surrounding the tubules. Large numbers of the same histiocytes were seen which were somewhat pigmented because of the brown pigment which is inherent in the epithelium of the epididymis (Fig. 6). They were abnormal cells and belonged to the same cell series as those we had seen before.

We are now faced with the peculiar picture and have to tie it together. Was this typical Hodgkin's disease, and, if not, why not? I am very pleased Dr. Rosenthal made a diagnosis of lymphoma because this is a difficult diagnosis to make. However, this is an entity which for some reason or other has remained rather obscure. Its name is histiocytic medullary reticulosis and Robb-Smith and Scott first described this over twenty years ago (1). Robb-Smith, who is one of the leading British pathologists, developed a rather elaborate system of classifying the diseases of the reticular system or lymphoreticular system. One of the things which can be extracted from this perhaps overelaborate classification is this disease entity (Table II). All the reported cases are in adults.

The sex is equally distributed. Onset characteristically is rather acute or subacute. The mean duration is four months. In our case duration was about two months. It is a malignant disease and its symptomatology is very well illustrated in our case. Icterus was present with splenomegaly, hepatomegaly and fever. We do not have too much information about weight loss. Some people do have serous effusions. Another important finding is that of severe anemia, sometimes with normoblasts, and thrombocytopenia, sometimes with purpura. Of 13 cases the mean splenic weight reported was 860 Gm. Our patient's was 850 Gm. Histologically, all the criteria are met by the present case. Progressive and multifocal proliferation of histiocytes and their precursors in lymph nodes, spleen,

TABLE II

*Clinical and Pathological Features of  
Histiocytic Medullary Reticulosis (Scott and Robb-Smith 1939)  
Giant Cell Reticulosis (Israëls 1953)*

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Clinical features:	<p><i>Age:</i> middle life.</p> <p><i>Sex:</i> equally distributed.</p> <p><i>Onset:</i> acute or subacute.</p> <p><i>Duration:</i> mean duration four months.</p> <p><i>Symptomatology:</i> asthenia, weight loss, icterus, splenomegaly, hepatomegaly, fever, serous effusions.</p> <p><i>Laboratory findings:</i> severe anemia with circulating normoblasts, thrombocytopenia (purpura), leukopenia, erythroid hyperplasia of marrow.</p>
Pathological features:	<p>Enlargement of lymph nodes, liver and spleen (860 Gm mean weight).</p> <p>Progressive and multifocal proliferation of histiocytes and their precursors in lymph nodes, spleen, liver, bone marrow, myocardium, lungs, kidneys, etc. These cells have phagocytic properties and in the spleen are packed with red cells.</p> <p>"Giant cells" resembling those seen in Hodgkin's disease are also present. Acute necrosis and fibrinous exudate are characteristic. Fibrosis and eosinophiles are absent.</p>

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liver, bone marrow, myocardium, are present. In certain areas, particularly in the spleen, where they are in contact with blood channels, these cells have marked erythrophagocytic properties and in this way contribute to the anemia. The giant cells, the reason why Israëls coined the name of giant cell reticulosis, are not diagnostic and should not be used to make the diagnosis of Hodgkin's disease because other features of the disease are absent (2). Acute necrosis and fibrinous exudate are found but fibrosis and eosinophiles are not. This disease probably is not recognized more frequently because most instances have been misdiagnosed as forms of Hodgkin's disease with severe hemolytic anemia and icterus. Nevertheless, it is a rare disorder. There are probably not more than twenty reported cases (1 to 4). However, the next time you are faced with an elderly patient who has fever, jaundice, and an acute anemia not necessarily with any lymph node enlargement but with hepatomegaly and splenomegaly,

you should think of histiocytic medullary reticulosis. In the lymph node biopsy, the chances are that characteristic histological changes will be found. Treatment is unsatisfactory. It is a relentless and quickly fatal disease.

*Question:* Can the diagnosis be made from a biopsy of the liver?

*Dr. Zak:* The atypical histiocytes together with the clinical course should enable one to make the diagnosis.

*Dr. Rosenthal:* An entity is recognized hematologically that is far afield from this one clinically. It is called reticulum cell leukemia in which a large spleen, thrombocytopenia, anemia, leukopenia or aleukemic bone involvement are found. In contrast to our present patient, a very chronic long course is followed.

*Dr. Zak:* Do these cases have a leukemic blood picture?

*Dr. Rosenthal:* Not necessarily. Sometimes the picture is that of the aleukemia type with 1 or 2 per cent of these cells. Occasionally patients will have an abundance of these cells. The characteristic of the cell is that its nucleus is to one side with abundant cytoplasm which tends to separate. I wondered whether or not that might not be the chronic equivalent of this particular disease.

*Dr. Zak:* The longest case of this malady in the literature had a course of one year. The great majority of them are much less, ranging from one week up to a year. The disease which Dr. Rosenthal just mentioned is a more chronic one and histologically I would not necessarily equate them. Monocytic leukemias and reticuloendothelioses, of course, exist. They are not too well defined a group and there may be some overlapping. However, here tremendous splenomegaly is present with a very impressive erythrophagocytosis in the spleen not seen in any other disease of the lymphoreticular tissue.

*Question:* How often does one see hepatic coma in this condition or other lymphomatous diseases involving the liver, and what is the mechanism?

*Dr. Zak:* I cannot answer your first question because I do not have the figures available. The second question is difficult to answer. We all have seen patients with lymphomas who become icteric with laboratory features of both obstructive and hemolytic jaundice and who may even clinically show hepatic failure. This probably is the result of some toxic substance but its origin cannot be localized to any particular place in the liver.

*Question:* How do you account for the lack of reticulocytosis in the face of marked hemolysis?

*Dr. Rosenthal:* It possibly might be accounted for on the basis of some marrow infiltration, although apparently the marrow was not extensively infiltrated. Infrequently in patients with lymphomas who have active hemolytic processes, the reticulocyte response is very slight. When that occurs, we say that part of the mechanism for anemia in such patients is due to blood destruction and part due to a delivery block, so that even though the patients should have a reticulocyte response, they do not because of the suppressive effect of the splenic enlargement.

*Dr. Zak:* There is one more point of interest. Ordinarily erythrophagocytosis in the spleen is accompanied by a good deal of iron pigment. Here, despite excessive erythrophagocytosis, iron pigment was almost completely lacking.

We have to assume that these abnormal cells, although very active in destroying red cells, were unable to handle the pigment afterwards, and, therefore, probably not enough iron was available again to form new hemoglobin.

*Dr. Rosenthal:* This man also may have had gastrointestinal bleeding, perhaps from an ulcer. Possibly, he actually may have been iron deficient. Though he had a breakdown due to hemolysis with the iron being re-utilized for hemoglobin synthesis not enough may have been present to enable the red cells to get out of the blood marrow. Is there any particular material contained in the histiocytes?

*Dr. Zak:* It depends on their location. The ones in the epididymis contained the brown pigment of the epididymis. Those in the lymph nodes did not contain anything demonstrable. Those in the spleen which were exposed to open circulation were very active in erythrophagocytosis.

*Final Diagnosis:* HISTIOCYTIC MEDULLARY RETICULOSIS WITH INVOLVEMENT OF LIVER, SPLEEN AND LYMPH NODES.

*Note:* This case is to be published: Zak, F. G., and Rubin, E. Histiocytic Medullary Reticulosis, *Am. J. Med.*, in press.

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# *Radiological Notes*

## USE OF A HALF-INCH BARIUM TABLET TO DETECT MINIMAL ESOPHAGEAL STRICTURES

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*New York, N. Y.*

In a previous note on "contraction rings" at the esophagogastric junction, the use of a compressed barium tablet\* one-half inch in diameter was briefly mentioned (1). In addition to demonstrating the presence of a significant narrowing by failure to pass, a tablet of known diameter furnishes a simple method of measuring the true size of the residual lumen at the site of a ring or a stricture. The tablet is flattened from side to side in order that patients may swallow it without difficulty. When held up proximal to a stricture, the patient complains of no special discomfort and fluid easily passes around the tablet. Within half an hour, the tablet will disintegrate and the fragments pass without difficulty. The diameter of half an inch was selected because it corresponds to the external diameter of a 36 French esophagoscope, the size which has been in routine use for esophagoscopy for many years. Transient delay particularly in older individuals at the level of the arch of the aorta or above the hiatus is often seen but a swallow or two of fluid carries the tablet distally without difficulty. The simultaneous visualization of the tablet and the constricted site makes calculation of the diameter of the constriction simple since the magnification factor is directly determined from the known size of the tablet. In inches, the true diameter of the narrowed site is one-half of the ratio of its measured value on the film to the measured value of the tablet.

The tablet described above has now been in use for a period of about five years and has proved its value in many instances. It has been of greatest use in patients who complain of dysphagia but in whom questionable or no definite findings are discovered by conventional methods (Fig. 1 A & B). In patients who refuse to drink sufficient amounts of barium, obstruction to the passage of the pill may nevertheless indicate the presence of important esophageal disease as the cause of symptoms. The difficulties of securing satisfactory films showing complete filling of the pharynx and cricopharyngeal area often make roentgen diagnosis in this region difficult. In such instances (Fig. 2 A & B) failure of the pill to pass this site freely may be sufficient evidence to warrant further studies, for example, by motion picture techniques. The original assumption that, if a tablet of this diameter passes through the esophagus without delay, dysphagia is not likely to be on an obstructive basis has not been contradicted by further experience.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

\* Manufactured by the Vitarine Co. Inc., Manufacturing Chemists, 625 West 55 Street, New York, 19, N. Y.



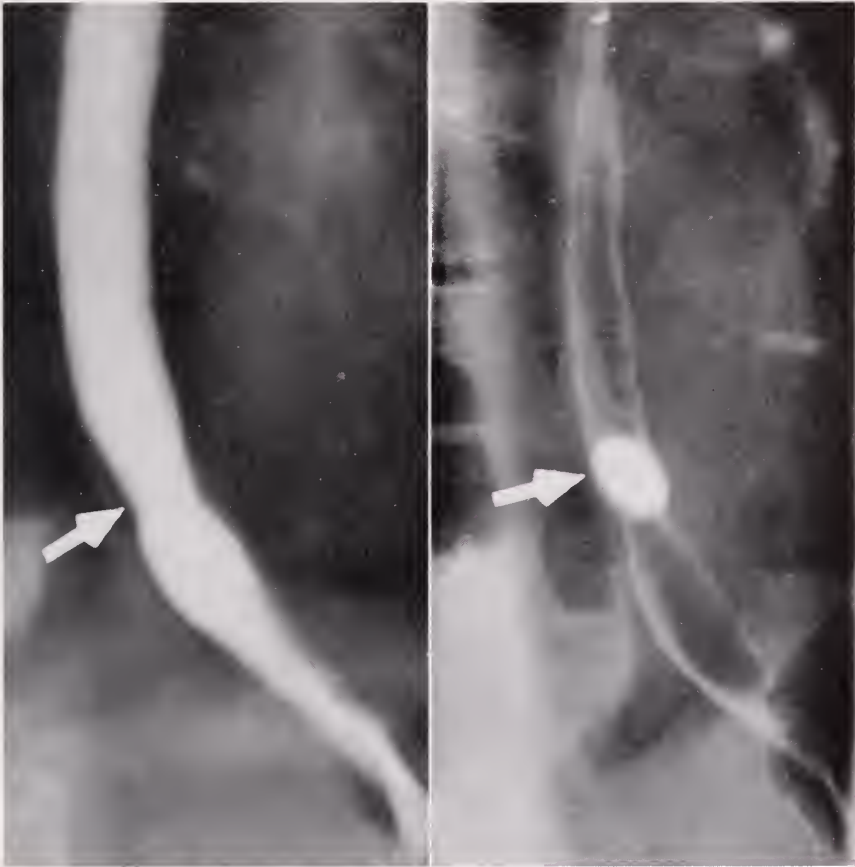


Fig. 1A. Barium swallow shows a faint shallow circumferential indentation (arrow) a short distance above the diaphragm to which little attention might be ordinarily paid.

Fig. 1B. The half-inch barium tablet (arrows) was obstructed a short distance above the diaphragm and did not pass until spontaneously fragmented. This was a rather elderly man who had been treated for two years for peptic esophagitis with a half dozen dilatations. Severe local narrowing had been previously present at the site of tablet obstruction. Dysphagia which had been marked was almost gone at the time of this examination.

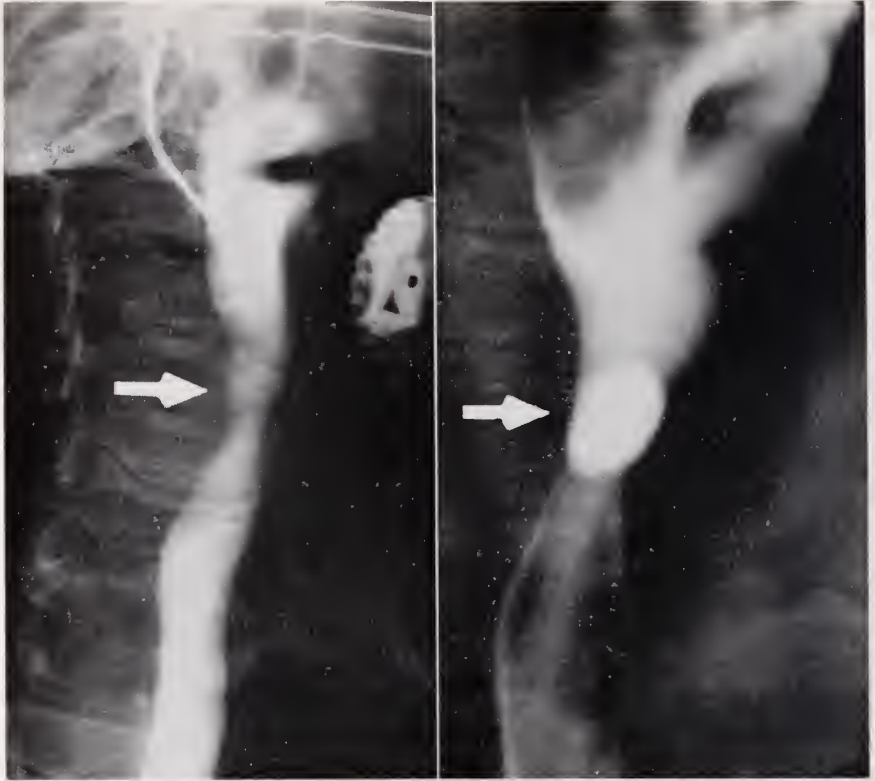


Fig. 2A. Examination of the pharynx and upper esophagus shows a minimal funnel-shaped type of narrowing (arrow) in the cricopharyngeal region.

Fig. 2B. A tablet was obstructed in the distal pharynx and failed to pass despite the administration of several glasses of water. Subsequent motion picture studies demonstrated persistent narrowing in this area.

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#### CASE NO. 126

This was the first admission of a 48 year old white male with a history of diarrhea and rather massive rectal bleeding for three days. The diarrhea consisted of five to ten loose lowel movements a day and showed, in addition to blood, some mucus. The patient complained also of slight anorexia but not of vomiting, nausea or fever. Except for occasional low abdominal cramps, there was no pertinent previous history. Examination on admission showed a mildly dehydrated male who did not appear to be markedly acutely ill. There was mild right lower quadrant tenderness without rebound or guarding. Rectal examination was negative. No stool was found in the rectum. Temperature was 99

degrees and during his short stay in the hospital did not go over 99.2. Hemoglobin was 15 Gm per cent, white blood cell count was 8,800 cu mm with a normal differential. The urine was normal. Stool was 4+ guaiac. Sigmoidoscopy was performed and was normal up to 6 inches. Stool cultures showed nothing specific.



Case 126, Fig. 1A. Barium enema examination shows very bizarre irregular distensibility of the right side of the colon with persistent thick haustral folds. The haustral pattern of the transverse colon as far distally as the splenic flexure is also abnormal with multiple small folds which may indicate "irritability".

The patient was treated with chloromycetin and sulphasuxadine as well as paregoric and atropine and rapidly improved. He was discharged a week after admission.

Barium enema examination on the day of admission (Figs. 1A, 1B) showed distinct lack of normal distensibility of the right side of the colon with irregular coarsely nodular mucosal thickening. Discrete ulceration was not demonstrated but the mucosal pattern was hazy and indistinct. Changes of lesser severity in-

dicating thickening of the mucosa as well as some irritability of the bowel were seen as far as the splenic flexure. There were numerous diverticula in the left side of the colon and evidence of irregular contractility of the descending colon and



Case 126, Fig. 1B. Evacuation film shows in somewhat better fashion the marked irregularity of contour of the irregularly contracted right side of the colon with hazy thick or coarsely nodular mucosal pattern. These mucosal pattern changes extend into the transverse colon. Evacuation was incomplete and irregular. In the descending colon and sigmoid, there are numerous short segmental contractions which indicate functional abnormalities. The ileocecal valve region is similarly involved.

sigmoid. Re-examination six days later (Fig. 2) showed irregular filling with some irritability of the right side of the colon but the general appearance, pattern and behavior did not appear to be too remarkable.

The findings on the original barium enema examination in this patient are quite remarkable and appear to indicate a severe inflammatory process. The rapid clinical improvement as well as improvement in the roentgen features



were therefore surprising. The disease process apparently consisted of an acute colitis which appeared to spare for all practical purposes the left side of the colon and therefore can be referred to as an acute "right-sided" colitis. No specific etiology was found although this possibility is not completely excluded. This case



Case 126, Fig. 2. Barium enema examination done six days after the original examination shows irritability in the region of the sigmoid and hepatic flexure. The ascending colon and terminal ileum are normally distensible. The general appearance and pattern are obviously considerably improved.

is in marked contrast to chronic right-sided ulcerative or granulomatous colitis which is irreversible.

*Case Report:* ACUTE TRANSIENT RIGHT-SIDED COLITIS, ETIOLOGY?

#### CASE NO. 127

This was the first observation of a 38 year old married female who had no complaints until about six months prior to examination. She began to complain at that time of recurring episodes of epigastric pain which usually lasted five to ten



minutes. These episodes were not related to meals and did not occur at night. Eructation was increased and furnished some relief. These episodes of pain became more frequent and began to be associated with vomiting of bile-stained material. She was anorectic and lost more than forty pounds in weight in a period of six months. Except for weakness, she had no other complaints. There had been no change in bowel habits. Physical examination was not contributory. It was obvious, however, that the patient had lost considerable weight. Hemoglobin was 12 Gm per cent. White blood count was 6,600 per cu mm with a normal differential count. Sedimentation rate was 12 mm per hour. A test meal showed free acid up to 26 units and a total acid up to 34 units. There was no blood in the gastric contents or in the stool. At the beginning of the test meal, about 80 cc of mucoid fluid was aspirated from the stomach. There was no bile in this. The clinical impression was possible duodenal ulcer with incomplete pyloric obstruction.

Barium meal examination was done on three occasions over a period of nine months and again about three years after the original observations. The findings on each occasion were essentially identical. The stomach always contained a considerable amount of excess secretions despite the fact that the patient assured the examiner that she had fasted for at least eight to twelve hours prior to the examinations. In association with the persistent gastric contents, the stomach did not contract normally and peristaltic activity particularly in the proximal two-thirds of the stomach was diminished. The rugal pattern in the antrum of the stomach was somewhat exaggerated and irregular with multiple transverse folds (Fig. 1A). A rugal pattern, however, was not demonstrable in the remainder of the stomach where an amorphous appearance of mottled barium irregularly adherent to the surface was evident. In places, very fine mucosal wrinkles or ridges could be seen with a coarse interlacing pattern of the mucous membrane. The most remarkable feature of the examination was evident when the stomach was filled with barium (Fig. 1B). Along both the lesser and greater curvatures throughout most of their extent, there were innumerable minute, somewhat pointed projections from the contour which were about one millimeter in depth and gave a rather symmetrical finely scalloped or serrated appearance. It appeared tempting to call these innumerable projections small ulcerations or erosions but there was evidence suggesting that they represented simply the profile manifestations of crevices in the abnormal mucous membrane surface (Fig. 1C). No filling defect or evidence of a gross ulcer crater could be demonstrated. The duodenal bulb and duodenal sweep did not appear to be remarkable. The small bowel was examined at frequent intervals and was within normal limits. The stomach emptied slowly. About half of the administered barium was retained for a period of three hours.

The roentgen impression was that of a chronic gastritis and gastroscopy was recommended. On gastroscopy, it was obvious that the mucosa was completely abnormal. There was a complete absence of rugal folds. The surface was dull, pale red and coarsely nodular with multiple patches of adherent opaque yellow exudate. No discrete erosions were evident. In the fundus of the stomach, the nodular mucosa was considerably coarser and presented an appearance which

has been referred to as an "état mamelonné." The diagnosis of the gastroscopist was "chronic hypertrophic gastritis." A brush examination for gastric cytology was performed and there was no evidence of cancer cells. An attempt to do a blind suction biopsy of the stomach was not successful.



Case 127, Fig. 1A. Administration of a small amount of barium demonstrates that the stomach is persistently distended with secretions and gas. Thick, somewhat irregular transverse folds are seen beyond the re-entrant angle but no evidence of rugal pattern is seen more proximally. Thin lucent lines (in area between arrows) indicate ridges or wrinkles in the surface of the mucous membrane and are not rugae.

Since the original observation, this patient has been treated symptomatically but has not shown any significant improvement over a period of more than three years. However, there has been no deterioration in the patient's condition and no reason to suspect any disease process independent of the stomach.

The opinions as to the significance and varieties of "gastritis" differ a great deal. Efforts to correlate roentgen findings with gastroscopic and biopsy find-

ings of the gastric mucosa in diffuse inflammatory conditions of the stomach have not been entirely successful. The status of the polypoid or verrucous type of gastritis which presumably is suggested by the term "état mamelonné" is also a



Case 127, Fig. 1B. With filling of the stomach, there is no limitation of distensibility, rigidity or filling defect. Distensibility, if anything, is somewhat increased (in contrast to the findings with a diffuse infiltrating carcinoma). Innumerable spiculations are present along most of the lesser and greater curvatures which produce markedly serrated contours.

subject of controversy. There is only an occasional patient with gastritis who shows the striking roentgen findings demonstrated in this patient. The gastroscopic findings confirm the suspicion that the innumerable spiculations evident on roentgen examination do not represent ulcerations but are a manifestation of the altered mosaic pattern of the mucous membrane. The absence of blood

in the gastric aspirate or in the stool is consistent with this interpretation. It therefore is not correct to refer to this "roentgen" type of gastritis as erosive gastritis. As a matter of fact, in the instances that we have seen that have been



Case 127, Fig. 1C. With somewhat less barium in the stomach, the irregular, zigzag transverse crevices in the mucous membrane are evident (area between arrows) and can be followed to the curvatures where they become continuous with projecting spicules.

called erosive gastritis associated with marked gastrointestinal bleeding, the "erosions" have not been demonstrable by roentgen examination.

*Case Report:* CHRONIC GASTRITIS—"ÉTAT MAMELONNÉ"; DIFFERENTIATION FROM EROSIVE GASTRITIS.

#### CASE NO. 128

This was the first admission of a 51 year old white female with the chief complaint of epigastric pain. Three years prior to admission, because of this pain, a barium meal was done and the diagnosis of a duodenal ulcer was made. The pa-

tient was treated with antacids and a suitable diet with fair symptomatic relief. Two years prior to admission, she began to complain of episodes of severe epigastric pain associated with excessive sweating, nausea and occasional vomiting.



Case 128, Fig. 1. An elongated ovoid, sharply demarcated filling defect is seen in the distal portion of the descending duodenum (between arrows). The fold pattern over the distal portion of this tumor appears relatively intact though tortuous and irregular. No definite mucosal pattern is seen over the more proximal portion. There was no delay to the passage of barium through this area, no evidence of rigidity or of extrinsic compression. The appearance of this defect did not change during the various phases of filling and emptying of the duodenum.

These episodes were relieved by morphine injections. She was hospitalized elsewhere after a typical attack of this type and subtotal gastrectomy was recommended. However, on medical therapy, she improved until two weeks prior to admission when, during the middle of the night, she was awakened by another episode of severe epigastric pain associated with nausea, vomiting and diaphoresis. She was admitted for evaluation for surgical therapy. Examination on ad-



mission showed a well developed, somewhat obese female in no distress. Physical examination was essentially negative. Barium meal examination showed some irritability of the duodenal bulb but no evidence of constant deformity or ulceration within it. However, in the distal descending duodenum (Fig. 1), there was an elongated, ovoid filling defect which was sharply demarcated, particularly proximally. The proximal part of this defect showed no distinct mucosal pattern but some irregular folds appeared to cover this defect distally. There was no obstruction to the flow of barium through the duodenum despite the fact that most of the lumen of the duodenum at this site appeared to be occupied by the mass. There was no evidence of extrinsic pressure on any portion of the duodenal sweep. The impression from the roentgen examination was that this represented an intramural tumor, possibly a myoma. A lipoma did not seem likely because of failure of the mass to change shape in different stages of duodenal contraction. On this basis, the patient was explored and a rather soft mass was felt in the descending duodenum near the ampulla. The duodenum was opened and a polypoid mass about 4 x 2 cm in size was exposed. Frozen sections of the mass were reported as unequivocally benign. The polyp was removed with considerable care because of its close association with the papilla. Paraffin sections confirmed the fact that the tumor was a benign polyp and demonstrated that it was papillomatous in character. Pathological report was "papillary adenoma—no evidence of malignancy." The patient's postoperative course was satisfactory.

Benign tumors of the duodenum beyond the bulb are most commonly intramural lipomas or myomas. A papillary adenoma in this region is uncommon. A tumor of this type is presumably related to the villous tumors most commonly seen in the colon.

*Case Report:* PAPILLARY ADENOMA OF THE DESCENDING DUODENUM.

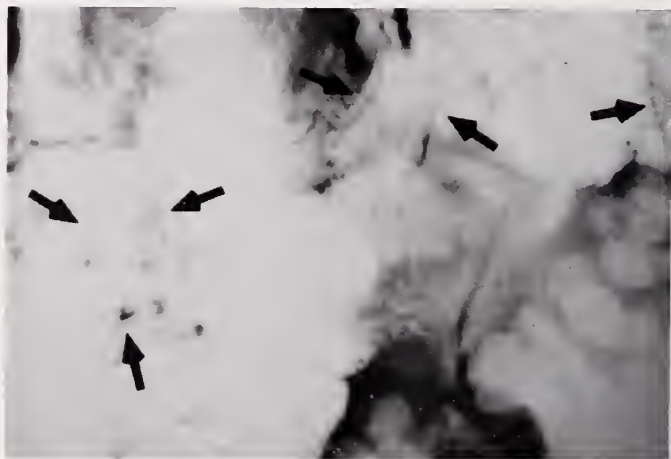
#### CASE NO. 129

SUBMITTED BY CHARLES M. NEWMAN, M.D., AND BERNARD S. ARON, M.D.

This was the first observation of a 20 year old white male college student who was born in Mexico and lived there until his 17th year. He came to this country to obtain further schooling. He presented with the chief complaints of sleepiness during his classes and muscular aches after exertion for a period of seven months. Physical examination was not remarkable. Laboratory findings were not contributory except for a moderate eosinophilia. There was no evidence of hypothyroidism; the blood protein-bound iodine was high normal. Total cholesterol was normal. Basal metabolic rate was plus 6 per cent. The boy was aware that he was carrying a tapeworm because occasionally he would note isolated segments (proglottids) in the stool. He never noted a long chain of such segments.

Barium meal examination showed no abnormality in the esophagus, stomach or duodenum. However, in many segments of the small bowel (Figs. 1A, 1B), there were long, uniform, sharply outlined, linear defects about 2 mm in width. The suggestion was made that these defects represented the tapeworm. However, this suggestion was received with some skepticism because of the possibility that the linear defects were due to small bowel folds. In places, however, they appeared to be parallel to the long axis of the lumen and thicker than

normal folds in distended small bowel. By coincidence, at the same time, barium studies (Fig. 2) were done on a dog who showed at necropsy a tapeworm (*Taenia saginata*?) 6 feet in length in the small bowel. The appearance, while more strik-



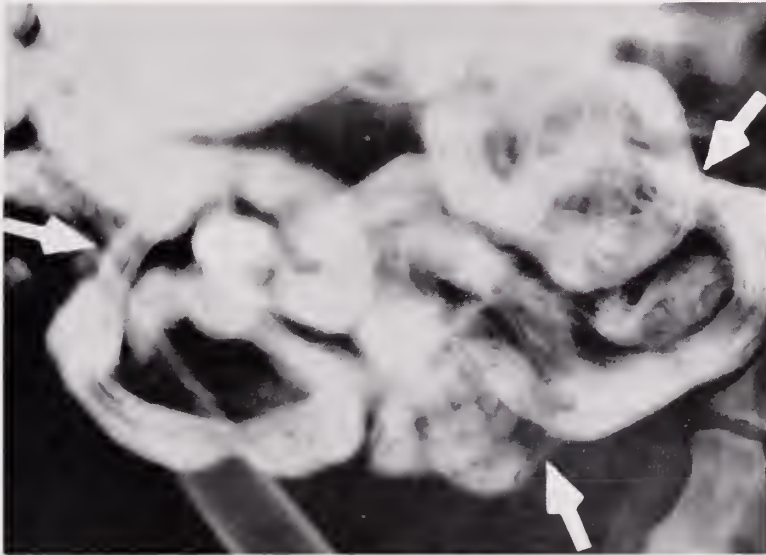
Case 129, Fig. 1A. In various loops of small bowel, linear defects (arrows) about 2 mm in width are seen which do not conform to the usual course of folds. In front of the sacrum (between lower arrows), a coiled linear defect is seen.



Case 129, Fig. 1B. The defects (arrows) persist during later phases of the small bowel examination.

ing than that seen in the patient, was similar and indicated that the diagnosis of tapeworm infestation roentgenologically was possible. Previous efforts to rid the boy of the tapeworm had been unsuccessful. On this occasion, however, following atabrine and a saline purge, a tapeworm approximately 20 feet in length was passed per rectum. The parasite was identified as *Taenia saginata*. Unfortunately, a repeat barium meal has not been feasible.

The recognition of the presence of a tapeworm in the intestinal tract on roentgen examination is a rare occurrence. Schinz *et al.* refer to findings similar to those in this patient but no illustration is furnished (1). Hamilton recognized the presence of a tapeworm which proved to be *Taenia saginata* in the distal ileum after retrograde filling by barium enema examination (2). He described it as a "long, ribbon-like, filling defect". Since the worm is quite flat, measuring about 1 or 2 cm in width and 2 or 3 mm in thickness, only the portions of the worm seen in profile would be recognized. If it happened to be caught en face, it would be completely obscured by the surrounding barium. A variety of appearances



Case 129, Fig. 2. Small bowel examination in a dog with a 6 foot tapeworm shows long continuous linear filling defects.

could occur as a result of the variations in the plane of projection of the worm as compared with the direction of the x-ray beam. This would explain the apparent discontinuities in the linear filling defect. Irregular rounded defects due to coiling up of a portion of the worm or of a chain of segments have also been described. In contrast to the findings in the round worm (*Ascaris*), no barium will be visualized in the intestinal tract of the tapeworm since the intestinal tract is confined to each segment, does not traverse the entire length of the worm, and the intestinal pore is extremely small.

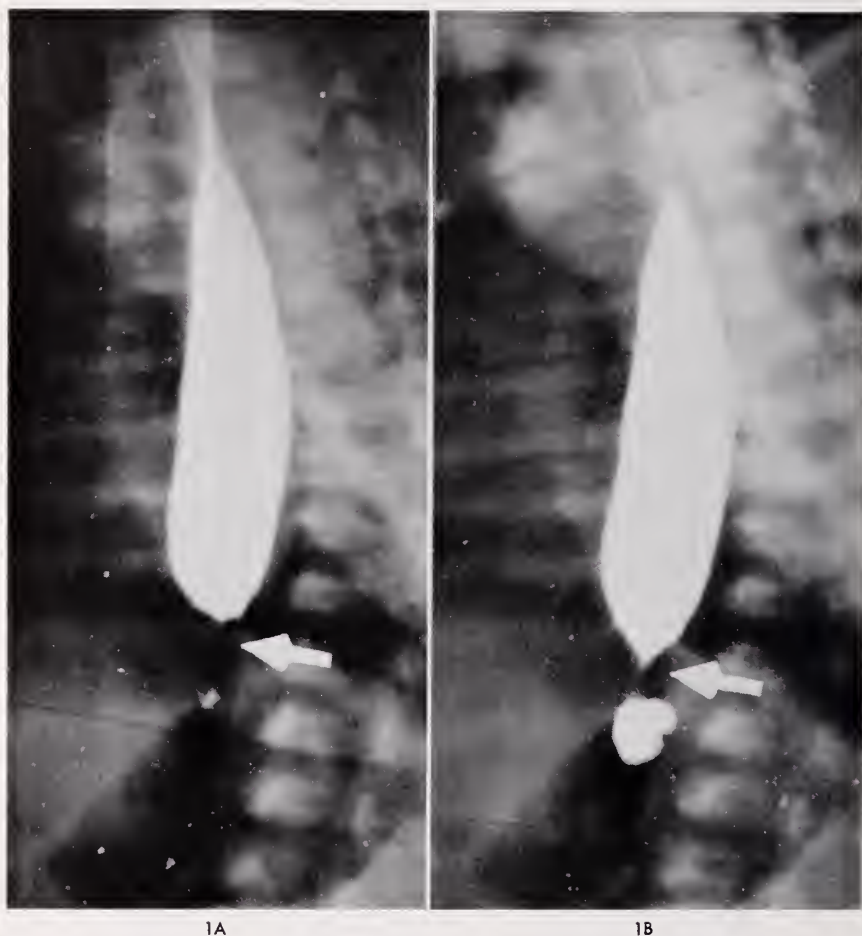
*Case Report:* ROENTGEN DIAGNOSIS OF TAPEWORM INFESTATION.

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## CASE NO. 130

A newborn male infant took every feeding poorly and showed excessive mucus and regurgitation. Bowel movements were decreased. Delivery had been uneventful and the child was otherwise not remarkable. A barium swallow was



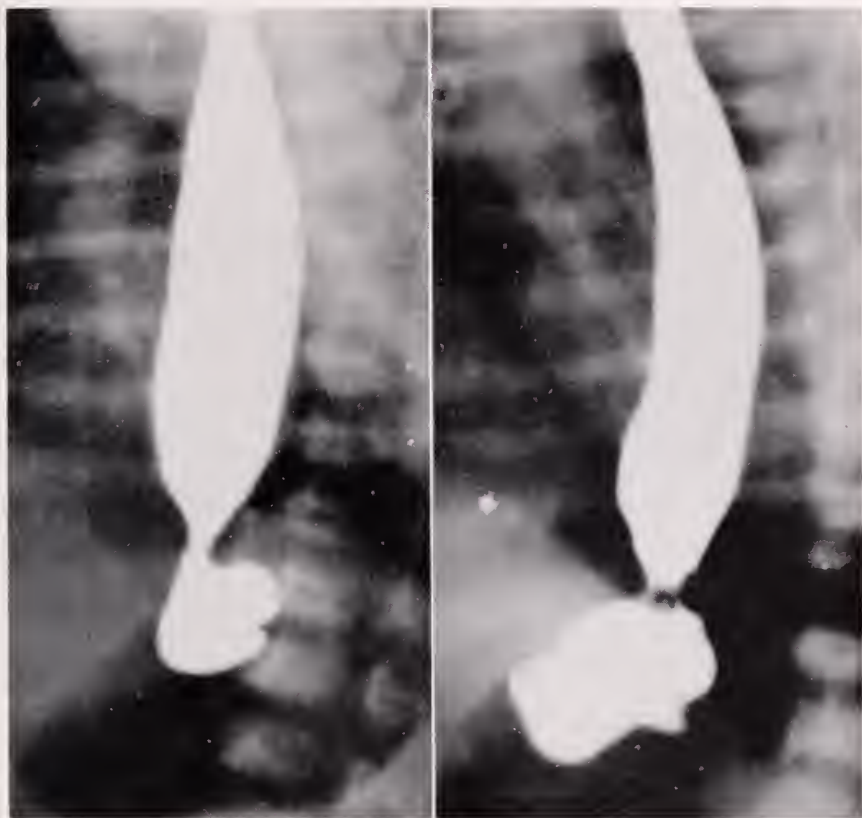
Case 130, Figs. 1A, 1B, 1C, 1D. Spot films showing excessively distended esophagus with persistent narrowing in the esophagogastric region. There was significant delay in the passage of barium into the stomach (Fig. 1A) as well as retention of barium in the esophagus for at least forty minutes. The maximum demonstrable diameter of the channel between the esophagus and stomach is shown in Figs. 1C and 1D.

ordered after five days to determine the presence of a vascular ring. Barium swallow was of considerable interest (Figs. 1A-1D). There was distinct delay to the passage of the conventional fluid barium water mixture into the stomach. Moreover, the esophagogastric junction was persistently but not rigidly narrowed. The esophagus above the diaphragm was unusually distensible. Films



made forty minutes after the administration of barium showed obvious retention in the esophagus. There was no evidence of reflux of barium from the stomach into the esophagus or of a hiatus hernia. No abnormality was seen in the stomach or duodenum and there was no evidence of delay in barium leaving the stomach.

In general, the appearance of the esophagus and esophagogastric region in this newborn was not unlike that seen in cardiospasm, *i.e.* achalasia, as seen in



1C

1D

adults. The functional nature of the changes was clear and re-examination after a short period was recommended. However, on antispasmodics, the child improved within a week and was discharged. The condition was therefore obviously not cardiospasm. For want of a better name, it may be designated as "spasm of the cardia." In contrast to "achalasia" in which the cardia is patulous, spasm in this region in the newborn is much less common. I am aware of one similar case with identical roentgen features and more severe clinical findings which also subsided in a matter of a couple of weeks. In this latter infant, a soft rubber tube had been passed into the stomach as a therapeutic measure.

*Case Report:* "SPASM OF THE CARDIA" IN A NEWBORN.



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SYMPOSIUM  
ON  
HYPERTENSION

Milton Mendlowitz, M.D.

*Guest Editor*

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## INTRODUCTION

The treatment of hypertension has been changing so rapidly that even those working actively in the field find it difficult to keep pace with every new development. These changes are not only affected by the availability of new modalities of therapy, but also by improvement in differential diagnosis and by continuing exploration of the mechanisms involved in the hypertensive process. These explorations influence our concepts of the disease process and hence our "therapeutic approach".

Not so long ago, the physician dealing with degenerative cardiovascular disease concentrated his attention on what was often the final common pathway of these diseases, namely congestive heart failure. Arteriosclerotic heart disease with congestive heart failure is still a common diagnostic catch-all and the attention directed toward ameliorating the sad lot of such patients is surely justified.

Recently, there has been a growing tendency to focus on the factors that usually bring the patient to this final phase about which we can do so little, and we try to treat the causes of acceleration of arterial disease. One of the most important of these causes is hypertension.

Hypertension itself, moreover, is an abnormal or diseased state into which many differing pathologic processes converge. What is more it may not only be a cause but also a result of arterial disease, thus perpetuating itself in cycles. Knowledge of mechanisms in this area is still chaotic although slowly advancing.

It is hence necessary, whenever confronted with the problem of treating hypertension, to differentiate so-called secondary from primary hypertension, always keeping in mind that in some individual cases more than one cause may contribute to the hypertension. The recognition of secondary hypertension usually depends on identification of the underlying cause. This is often not at all complex and requires only careful clinical evaluation. In some cases, however, it is most difficult even when all laboratory testing procedures are applied. The major causes of secondary hypertension are (1) renal disease, (2) adrenal cortical hyperplasia or tumor, (3) pheochromocytoma and (4) coarctation of the aorta. The renal causes can be subdivided further into the following categories: (1) chronic or acute glomerulonephritis, (2) chronic pyelonephritis, (3) diabetic glomerulosclerosis, (4) coarctation of the renal artery and (5) polycystic kidneys. Adrenal cortical disease also requires further definition as Cushing's syndrome or aldosteronism.

When all these cases of secondary hypertension are segregated, there still remains a large group approximating eighty per cent or more of the total in which no known underlying cause can be identified and these cases must therefore be classified as primary or essential hypertension. These patients often have a family history of hypertension and the condition is so common that it may adventitiously complicate any other type of hypertension with confusing frequency. What is more, essential hypertension tends eventually to destroy the kidney, which is one of the most vulnerable organs, with the development of complicating secondary renal hypertension. It is not unusual, moreover, for essen-

tial hypertension to produce secondary changes in the adrenal cortex and occasionally also in the medulla thus causing a complex of essential, renal and adrenal hypertension. To make matters worse, the kidneys of patients with essential hypertension are more susceptible to infection than normal, so that pyelonephritis may also complicate the entire clinical picture.

As for the mechanism responsible for the initial process in primary hypertension, this too is becoming clearer as time advances. The systemic arterial vasculature seems to be more reactive to constrictor stimuli in individuals with essential hypertension than in normotensive persons, although there is still some disagreement on this point. This phenomenon, however, has been demonstrated in the systemic circulation as a whole (1), and in the digital skin (2) and forearm muscle (3), the stimulus infused being L-norepinephrine. Similar hyperreactivity can be shown with angiotensin II as the stimulus (3, 4). The cold pressor reaction (5) may be a special instance of this since the normal pressor reaction involves the local elaboration of L-norepinephrine by sympathetic nerves. This hyperreactivity is demonstrable very early in the course of essential hypertension and may represent a cause of the disease. On the other hand, there are those who argue that it may be an effect of the generalized increase in resistance in hypertension (6-8). If it is a cause, it is not yet established whether the cause arises from faulty enzymatic breakdown of the stimulating chemical substance, or some chemical change indigenous to smooth muscle metabolism itself.

Another school of thought holds the view that changes in renal metabolism initiate the vasoconstriction which is characteristic of essential hypertension. Angiotensin II may be elaborated by the kidney and thus produce the disease, although this does not explain the vascular hyperreactivity to this substance. Altered handling of sodium by the kidney which is known to occur in hypertension (10-12) has also been evoked as a cause, although many observers consider this to be an effect of essential hypertension. Still another group impute the hypertension to altered adrenal cortical activity with special reference to aldosterone (13, 14).

Regardless of the mechanisms involved in the disease, therapy has progressed to the point where most patients with hypertension can have their blood pressures controlled and brought to normotensive or near normotensive levels. This is considered desirable in all patients with grade III to IV eye-ground changes, since in this stage the hypertension is often symptom producing and is a threat to life. What is more, therapy has been demonstrated by many observers to be effective in prolonging the life of such patients (15, 16). In patients with grade I to II eye-ground changes, however, the prognosis is often good and the evidence that therapy is of value is still inconclusive (16) and hence presumptive. Yet many observers believe in vigorous therapy for hypertension in any stage of the disease.

Within the last fifteen years a complex array of drugs has become available for the treatment of essential hypertension, many being replaced by better or different drugs in the same or in a different class within as little time as a few

years. These drugs have not only been effective in controlling the blood pressures of most patients with essential hypertension, but have increased knowledge of the mechanism of the disease.

The drugs fall into two general classes; those affecting the sympathetic nervous system and those whose primary action is not on the sympathetic system. In the former group are tranquilizers of various types, the Rauwolfia group of drugs, the ganglion-blockers, veratrum derivatives, monamine oxidase inhibitors, drugs affecting the postganglionic sympathetic nerves (such as bretylium tosylate and guanethidine) and drugs affecting the nerve endings such as dibenzyline. In the second group are chlorothiazide and its various congeners, aldosterone inhibitors and hydralazine, each of which probably has additional effects at different sites on sympathetic nerve function as well. In each of these groups there has been an enormous effort on the part of pharmacologists to find congeners with the greatest action at the smallest dosage, as well as with the fewest undesirable side actions and the most desirable duration of effect. The result in the clinic is a continuous shifting of therapy to so-called drugs of choice which often vary with the individual patient.

The low sodium diet has been largely replaced by the thiazide drugs and surgery confined chiefly to various types of secondary hypertension such as coarctation of the aorta, renal artery coarctation and tumors of the adrenal cortex and medulla. Sympathectomy and even adrenalectomy, however, still have their adherents and the former at least has a place in the treatment of certain recalcitrant individual patients for whom drug therapy is impractical.

In this symposium an attempt will be made to review the mechanisms, as well as the management of the known varieties of hypertension, presenting the most recent experience of various clinical observers and investigators. If the pace of development becomes accelerated or even remains unchanged, much of what is written here will no longer be applicable within a few years. Nevertheless, it is of interest to catch our breath, take stock, and determine our present position comprehensively.

*The Mount Sinai Hospital*  
*New York, October, 1960*

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## THE ETIOLOGY OF HYPERTENSION

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Mean blood pressure increases in the systemic arterial tree when the mean volume of blood which it contains is increased (1). This can be accomplished by increasing the output of the left ventricle or by decreasing the caliber of the small peripheral blood vessels, the most important of which in this respect are the arterioles. Because of the elasticity of the arterial walls, relatively small increments in volume are associated with relatively large increases in pressure. Theoretically, this effect could be enhanced by increased tone of the smooth muscle of the entire arterial tree, but although there is evidence that this does occur (2), some observers believe that the major function of the smooth muscle of large arteries is to adapt the vessels to changes in vascular volume (3). When the large arteries become sclerotic and their elasticity hence becomes impaired, there is an increase in pulse pressure. This is associated with a decrease in diastolic as well as an increase in systolic pressure, so that in its pure form large vessel arteriosclerosis produces no change in mean blood pressure. Mean volume, however, may be increased in this situation if the capacity of the arterial tree, especially of the aorta, has been increased because of the arteriosclerosis (4).

There is relatively little disagreement on how hypertension is produced by a variety of mechanical changes within the arterial tree, whether the hypertension be systolic as in arteriosclerosis or in aortic insufficiency or mean as in coarctation of the aorta. In aortic insufficiency the increased systolic blood volume and pressure is caused by the diastolic back flow into the ventricle (5), whereas in coarctation there is an abnormal mechanical resistance interposed in the aorta, compensated for to a variable extent by collateral circulation. Most modern measurements have revealed increased blood flow in coarctation, especially proximally, although compensatory vasoconstriction may also play a role (6, 7). If the coarctation is near the renal arteries, it is believed that the hypertension in these rare cases may be of "renal" origin (8). Distal to most coarctations, however, mean blood pressure and flow in the resting state are usually normal despite the mechanically produced decrease in pulse pressure. With exercise, however, vascular insufficiency may appear distal to the coarctation, especially in the muscles of the lower extremities (intermittent claudication).

Having disposed of these mechanical varieties of hypertension, we are left with the hypertension caused either by increased left ventricular output or by narrowing of the peripheral small blood vessels. There is some evidence that early

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Supported by grants from the American Heart Association and the National Heart Institute (H-1164).



in the course of so-called essential hypertension, cardiac output may be increased in some cases (9), but in established hypertension, nearly all workers are agreed that cardiac output is normal (10). The "resistance" therefore, of the peripheral blood vessels must be increased. Acute generalized vasoconstriction, however, produces not only an increase in blood pressure proximal to the vasoconstriction, but also a decrease in blood pressure distal to it and a decrease in flow. The normal cardiac output in hypertension can therefore be explained only by presuming an increased force of ventricular contraction sufficient to keep the cardiac output normal. The complex mechanisms responsible for this effect are poorly understood but that it occurs, is attested to by the hypertrophy of the left ventricle so characteristic of systemic arterial hypertension.

Let us now focus our attention on what is believed to be a major cause of arterial hypertension, namely an increase in "peripheral resistance" (11, 12). Since the viscosity of the blood is normal in hypertension (13), the contribution of this factor to "resistance" can be disregarded. It is to be noted, however, that small rises in blood pressure can be seen in polycythemia, although Gaisboeck's syndrome is believed to represent the coexistence of polycythemia vera and essential hypertension (14). In most cases of hypertension, however, the increase in "resistance" is caused by a decrease in small blood vessel caliber and it is pertinent to consider the possible physiologic and pathologic processes which might cause such narrowing. In fact, this is the nub of the problem of etiology.

One may thus consider (1) fibrinoid necrosis, (2) intimal edema, proliferation or both, (3) muscular hypertrophy and (4) functional vasoconstriction due to vascular smooth muscle contraction. Fibrinoid necrosis of small blood vessels is a late effect in essential hypertension and certainly not an initiating cause (15). Fibrinoid necrosis, however, may not always be apparent as an acute process and may manifest itself pathologically as an organized area indistinguishable from intimal proliferation. Intimal proliferation does occur in hypertension and it is not impossible that reversible intimal edema may also occur (16). This encroachment on the lumen of the small blood vessel with resultant hypertension is, however, a late manifestation of the disease (17). Hypertrophy of the media is another late effect of hypertension and the smooth muscular overgrowth may also encroach on the vascular lumen to some extent producing additional hypertension (18). Surely, however, muscle does not become hypertrophied *de novo* but as a result of increased work, indicating again what must be the earliest and the initiating process, namely increased functional vasoconstriction.

What is the evidence that such functional vasoconstriction is increased in hypertension? On the positive side the response to such drugs as reserpine and the ganglion blocking drugs can be cited. The decrease in blood pressure after administration of the latter drugs is greater in the hypertensive than in the normotensive group (19), although the ganglion blocking drugs also cause a decrease in cardiac output because of venomotor paralysis (20). When the blood vessels are visualized in the eponychium (21) or in the conjunctiva (22), vasoconstriction is increased in the hypertensive group. On the other hand, when neurogenic vasoconstriction is measured in the extremity, it may be found nor-

mal when measured in terms of "resistance" (23), but increased when measured in terms of "work of vasoconstriction" (24). These differences may be the result merely of technical and conceptual differences in physiological interpretation.

The weight of the evidence, therefore, favors the view that neurogenic vasoconstriction is increased in essential hypertension but there is also evidence that there is structural narrowing of blood vessels, presumably due to any combination of intimal edema or proliferation and muscular hypertrophy that may exist. The relation of the structural factors to the neurogenic vasoconstriction, however, is still unclear.

There are only two possible mechanisms for increased neurogenic vasoconstriction; one is increased frequency and intensity of neural firing and the other is increased reactivity of the smooth muscle to normal neural firing. Moreover, both factors can operate together. A third mechanism for producing vasoconstriction independent but imitative of neurogenic constriction, consists of the elaboration of chemical substances circulating in the blood which are identical with or act similarly to the natural neurohumor, norepinephrine.

The latter situation obtains of course in pheochromocytoma and may obtain in so-called renal hypertension. The kidney here is believed to elaborate a hormone which reacts with blood to become an extremely potent vasoconstrictor, angiotensin (25, 25a). In "pure" renal hypertension the major factor is usually an increase in intrinsic or nonneurogenic resistance (26), a finding equally compatible with the presence of a circulating vasoconstrictor or with some structural change in the vessel wall such as edema.

We may now return to the problem of neural firing versus reactivity in hypertension. The advocates of a psychosomatic etiology for essential hypertension must invoke increased neural firing, although this has never been demonstrated successfully in hypertension. One would have to demonstrate increased vasoconstriction in the absence of increased reactivity to impugn increased neural firing. Unfortunately, direct determination of nerve function in patients is not feasible with presently available techniques. Increased neural firing has been identified by the former technique, however, in Raynaud's disease. Yet Raynaud's disease is not ordinarily associated with hypertension. Is the neural firing increased more generally in hypertension and only acraly in Raynaud's disease?

That the blood vessels are more reactive to stimuli in hypertension, however, is amply demonstrated. One need only cite the cold pressor test (28) and the increase in systemic response to infused norepinephrine (29). It might be argued, however, that this is neurovascular, since it is uncertain whether the effect is mediated through the nervous system or represents a direct action on blood vessels. Recently, however, it has been demonstrated that in the digit (30) as well as in the forearm muscle (31), reactivity to norepinephrine, as well as to angiotensin, is increased in essential hypertension. This can only be demonstrated if flow as well as pressure is measured, and it is brought out strikingly if the measurements are converted to estimates of the work of vasoconstriction. These re-

actions can be elicited when nerve function is blocked by indirect heating and ganglion blockade or by ganglion blockade alone.

It has been reasoned by some workers (32-34) that such increase in vascular reactivity is caused by structural changes within the small blood vessels of the hypertensive subject such as intimal proliferation or smooth muscle hypertrophy. Still, it can be demonstrated that increased reactivity is present very early in the course of essential hypertension (26) without physiological evidence of intrinsic or structural encroachment on vascular lumina. Increased reactivity can also be demonstrated, for example, in mild toxemia of pregnancy attributable to latent essential hypertension (35). What is more, in Raynaud's disease where extreme structural changes take place, including thrombosis, and where smooth muscle hypertrophy is believed to occur, reactivity to L-norepinephrine is normal (27).

Certain concepts follow from the thesis that increased vascular reactivity is the earliest and the most consistent feature of essential hypertension. Any increase in neural sympathetic discharge such as might occur with emotional storms would produce an exaggerated effect on blood pressure in the hypertensive but not in the normotensive subject. Renal elaboration of angiotensin, moreover, from whatever renal disease is present would have a much greater effect in the person with underlying essential hypertension than in the normal person.

It may also be asked at this point, what the known and possible physiological and biochemical factors are that might influence vascular reactivity. It is now known, for example, that the normal stimulus to vasoconstriction is norepinephrine (36). Also, most substances known to cause vasoconstriction, even the most complex such as angiotensin, have an amine end group. Norepinephrine, moreover, is not only elaborated by sympathetic nerves and discharged at their endings, but it is also stored in the tissues (37). It is probably synthesized in the nerve from dopamine which in turn is derived through dopa from tyrosine (36). Cells have been described in the subcutaneous tissue which are believed to store catecholamines (38, 39).

If a large amount of casually produced norepinephrine is available and the stores are full, it has been shown that vascular reactivity to infused norepinephrine is low (40). On the other hand, if the organism does not elaborate norepinephrine and the stores are depleted, the vessels become much more reactive to infused norepinephrine. This effect has been attributed by pharmacologists to the availability or lack of availability of receptor sites on the smooth muscle cells. It is for this reason, that blood vessels become more reactive after sympathetomy and less reactive after repeated norepinephrine infusion or in the presence of a pheochromocytoma. It is apparent, however, that vasoconstriction is determined by vascular reactivity only if norepinephrine is available and that if it is not available, vasoconstriction will not occur despite increased vascular reactivity. Most drugs acting on the sympathetic nervous system, including guanethidine, deplete the tissues of norepinephrine by a variety of mechanisms (41, 42).

It is probably the concentration of norepinephrine available to the smooth muscle of both arteries and veins that determines the degree of vasoconstriction. When norepinephrine is depleted by inhibiting the function of the sympathetic nervous system, venules are affected as much as arterioles and according to some observers venules are predominantly affected since cardiac output, rather than peripheral resistance, decreases. Such measurements of resistance, however, tend to obscure effects on the arterioles since the venular pressure, especially in the upright position, is not known. An increase in such pressure ( $P_2$ ) could produce a decrease in  $P_1-P_2$  and hence a decrease in arteriolar resistance. Other errors may also make interpretation in this area treacherous.

Intrinsic reactivity to norepinephrine or any other vasoconstrictor substance is, however, best measured after inhibition of casual nerve function and depletion of stores (43). In normotensive subjects, reactivity as measured under these circumstances can be increased by glucocorticosteroids, whereas in hypertensive subjects these steroids have no effect on reactivity (44, 45). Also, reactivity in hypertensive subjects can be decreased by sodium depletion (chlorothiazide or its congeners) whereas in normotensive subjects such sodium depletion increases vascular reactivity (46). The sodium ion, therefore, is definitely implicated in vascular reactivity.

These facts can be explained only if one postulates a chemical basis for changes in reactivity. If an enzyme system is involved, this system is concerned either with destruction or binding of the stimulating substance, such as norepinephrine (42) or angiotensin, or it is part of the system involved in smooth muscle contraction as such. Sodium then may be an enzyme activator or a direct stimulant of smooth muscle contraction. In either case an optimum level is required above or below which the system functions poorly.

Hypertension produced by glucocorticosteroids may therefore affect the enzyme system directly, whereas aldosterone or desoxycorticosterone hypertension would be mediated via the effect of sodium retention on the same system.

The two known enzymes which inactivate catecholamines are monamine oxidase (47) and catechol O-methyl transferase (48). Monamine oxidase inhibitors, however, have little or no effect on vascular smooth muscle reactivity (49); in fact, instead of increasing blood pressure they decrease it in hypertensive subjects, probably by blockade at or beyond the sympathetic ganglia by mechanisms as yet unknown. There are also facts against implicating catechol O-methyl transferase. The blood and urine catecholamines are practically normal in hypertensive subjects (50, 51). Furthermore, the major metabolite of the catecholamines, vanillyl mandelic acid, is present in normal amounts in the urine of hypertensive subjects (52). This does not, however, negate a possible difference in the rate of degradation of norepinephrine in hypertensive subjects and this is under study. If this enzyme system is defective in hypertension, moreover, it would have to be considerably less specific than postulated, since patients with hypertension are more reactive to angiotensin as well as norepinephrine and, although the former has two projecting hydroxylated benzene rings and an amine end group, its chemical structure is quite different from the catechols. Moreover,



the system would have an automatic brake since as the concentration of norepinephrine increased in the tissues, it would tend to decrease reactivity by virtue of its effect in binding reactor sites. A possible unifying effect is the binding of catecholamines, the chemical mechanism of which is virtually unknown. We have not mentioned the enzymes involved in vascular smooth muscle contraction since this is indeed a dark area. A defect in either of these systems, however, would presumably be hereditary and would account for the hereditary transmission of essential hypertension (13, 53).

We may now ask how renal hypertension fits into this picture. In pure renal hypertension such as is seen in acute glomerulonephritis, or in more chronic glomerulonephritis or with polycystic kidneys, vascular reactivity is normal, whereas in essential hypertension it is always increased even if renal disease is present. The two possible mechanisms for hypertension in renal disease, therefore, are either the elaboration of a pressor substance such as angiotensin or retention of salt and water with hypervolemia and increased cardiac output. Edema of the walls of the small blood vessels may also play a role in such hypertension. It seems likely that in acute glomerulonephritis, hypervolemia is most important, whereas in chronic renal hypertension the other mechanisms may come into play. In any case, if angiotensin is present in the blood of a patient who already has the trait of essential hypertension, his blood pressure will be increased inordinately by the renal factor.

There are many obscure areas in this picture which are still poorly understood and defy explanation, such as the peculiar salt losing reaction of the kidney to salt loading in hypertension (54-56) and the role of hyperaldosteronism in late essential hypertension (57, 58). It is possible, however, that the major effect of hypertension, however produced, is the loss of salt from the kidneys by virtue of increased glomerular filtration and other factors. Loss of sodium from the body calls forth the secretion of adrenal aldosterone (59) as well as salt hunger, both of which may eventually increase the salt content of tissues, including that of the renal medulla. Also, the exact nature of renoprival hypertension is still obscure (60, 61). It seems unlikely, however, in view of the findings cited here, that essential hypertension is initiated by the kidney. It seems more likely that renal disease, both functional and structural, is an effect of the hypertension and, subsequently, a potentiating factor.

All the factors cited, including renal hypertension, tend to produce arteriolesclerosis which in turn also augments the hypertension and makes it relatively irreversible.

#### SUMMARY

Essential hypertension is probably initiated by hereditary hyperreactivity of vascular smooth muscle. The reactivity of this smooth muscle can be increased by glucocorticosteroids in normotensive but not in hypertensive subjects, whereas sodium depletion decreases reactivity in hypertensive and increases it in normotensive subjects. Reactivity is also increased by norepinephrine depletion, but vasoconstriction and hence hypertension probably depends on the



norepinephrine concentration in tissues, which is dependent both on the rate of production of norepinephrine and the rate of its inactivation. Most drugs, including guanethidine, acting on the sympathetic nervous system act by decreasing norepinephrine production in various ways. Essential hypertension is characterized by exaggerated vasoconstrictive and hence hypertensive response to any stimulus, such as norepinephrine (as produced by emotional factors), or angiotensin (as produced by complicating renal hypertension). In "pure" renal hypertension, vascular reactivity is normal and the increase in blood pressure is produced either by hypervolemia and an increase in cardiac output, or by vascular narrowing independent of neurogenic vasoconstriction. The latter effect is compatible with renal elaboration of a circulating pressor substance such as angiotensin, or with metabolic changes causing edema of the walls of small blood vessels, or both. All these factors produce arteriolosclerosis which contributes to the hypertension and is relatively irreversible. The chemical cause for the initiating vascular hyperreactivity resides either in an enzymatic defect in the system responsible for binding or inactivating norepinephrine, such as O-methyl transferase, or in an effect on the chemical complex responsible for vascular smooth muscle contraction itself.

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# SOME ASPECTS OF THE PATHOLOGY OF HYPERTENSION

## VASCULAR LESIONS IN EXPERIMENTAL AND HUMAN HYPERTENSION

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Although clinical knowledge of hypertension has its origin in the studies of renal diseases made by Richard Bright, experimental production of sustained elevation of blood pressure was first achieved a little over 25 years ago, by Goldblatt in his classic work on the effect produced by constriction of the renal arteries (1). Following this, hypertension was induced in animals in many ways, in most of which the integrity of the kidneys was attacked by various methods. Other approaches were also successful, such as administration of adrenal corticoids or pituitary hormones, sectioning of the pressor regulator nerves and induction of chronic cerebral ischemia.

Experimental hypertension is often accompanied by lesions of the blood vessels, particularly of arteries of various calibers. In many respects these lesions resemble those associated with human hypertension. In the present report, the vascular lesions encountered in several species of experimental animals will be reviewed and their nature and relation to human disease discussed.

### HYPERTENSION AND ARTERIAL LESIONS IN THE DOG

Goldblatt demonstrated that constriction of one renal artery produces temporary hypertension which could be abolished by removal of the affected kidney (2). Persistent hypertension developed if the opposite kidney was removed after the clamping of one renal artery, or if both renal arteries were constricted. The clamping of the renal arteries caused little functional or anatomical disturbance in the kidneys. The only vascular lesion observed even in long-standing hypertension was hyperplasia of the media of the arteries. However, if the constriction was carried to the point where renal insufficiency developed, a much more severe degree of hypertension ensued which was accompanied by extensive vascular changes. The latter developed rapidly, sometimes within a few days, and consisted of fibrinoid necrosis of arterioles and small muscular arteries (Fig. 1). Inflammation was not a conspicuous feature of these lesions.

Winternitz and his co-workers (3-5) studied various aspects of the relation of the kidney to the cardiovascular system. They observed that constriction of renal arteries, in addition to arteriolar changes, produced smooth muscle necrosis in the large vessels, in the muscularis of hollow viscera, especially of

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Supported by Research Grant (A-918), National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Bethesda, Md., by a grant from the Block Foundation, and by Dr. Eli Moschcowitz Fund.



the small intestine, and in the myocardium. Similar though more severe lesions could be produced by complete ligation of both renal arteries or of both ureters, but ligation of only one renal artery or ureter resulted in only minimal lesions. Bilateral nephrectomy caused only mild hypertension and minimal vascular alterations. If the life of the nephrectomized animal was sufficiently prolonged by peritoneal lavage or the application of the artificial kidney, severe hypertension and vascular lesions similar to those induced by other methods ensued (6). Changes of a more chronic nature such as subendothelial fibrosis, hyalinization and endothelial proliferation could be observed in dogs who remained alive for several weeks (7, 8).

Somewhat different vascular lesions were obtained by combining severe renal damage (bilateral nephrectomy, administration of uranium salts) with a high fat diet (9). These lesions were characterized by deposition of large amounts of metachromatic material in the damaged aortic media (mucioarteritis) (10). This was associated with mild hypertension. Necrotizing arteritis of medium-sized vessels has seldom been reported in the dog. It was observed in a few animals after silk-wrapping of the kidneys (11). In spontaneous chronic nephritis with azotemia, muscular arteries showed medial hypertrophy and arterioles showed fibrinoid necrosis (12).

Arterial and arteriolar lesions have also been produced without direct attack upon the kidneys by injection of pressor substances, such as adrenalin and N-amylamine (13, 14). In the aorta, hemorrhage and necrosis of the media occurred and in various organs including the kidneys there was segmental necrosis of small muscular arteries. Sometimes this necrosis was accompanied by inflammation of varying severity. Prolonged administration of small doses of adrenalin resulted in degeneration of smooth muscle fibers in the aortic media (15). Forceful intra-arterial injection of a large amount of blood was followed by the appearance of lesions similar to those produced by adrenalin injection (14). Neurogenic hypertension induced by sectioning of the pressor regulators caused only mild vascular lesions (medial hyperplasia and degeneration) even after a period of years (16).

#### HYPERTENSION AND ARTERIAL LESIONS IN THE RAT

Hypertension and vascular lesions can be produced in the rat by manipulation of only one kidney (2), although a considerably higher incidence and more severe damage result from bilateral manipulation (17). Compared with the dog, the rat exhibits a greater variety of vascular lesions. Some of these lesions are similar to those seen in the dog, such as fibrinoid necrosis of arterioles and necrosis of smooth muscle in the media of large and medium-sized blood vessels and necrosis of the muscularis of hollow viscera. In addition, the rat also shows arteritis of medium-sized and small arteries, e.g., the mesenteric artery and its branches.

Contrary to what happens in the dog, in the rat the vascular lesions bear a relationship to the method of production. When hypertension was caused by constriction of renal arteries (18) or of the aorta between the renal arteries (19), by

ligation of a renal artery (20) or of one of its major branches (20, 21), by encapsulation of the kidneys (22) or by a figure-of-8 ligature (23, 24), the outstanding vascular lesion was necrotizing arteritis of medium-sized and small arteries (Fig. 2). In all of these experiments there was interference with the renal circulation sometimes to the point of actual death of tissue. Fibrinoid necrosis of arterioles was not conspicuous unless there was accompanying renal insufficiency (19) (Fig. 3). When hypertension was produced by bilateral renal ablation, the main lesion was cytolytic necrosis of smooth muscle fibers in the media of large arteries (Fig. 4) and of those of hollow viscera, and also necrosis

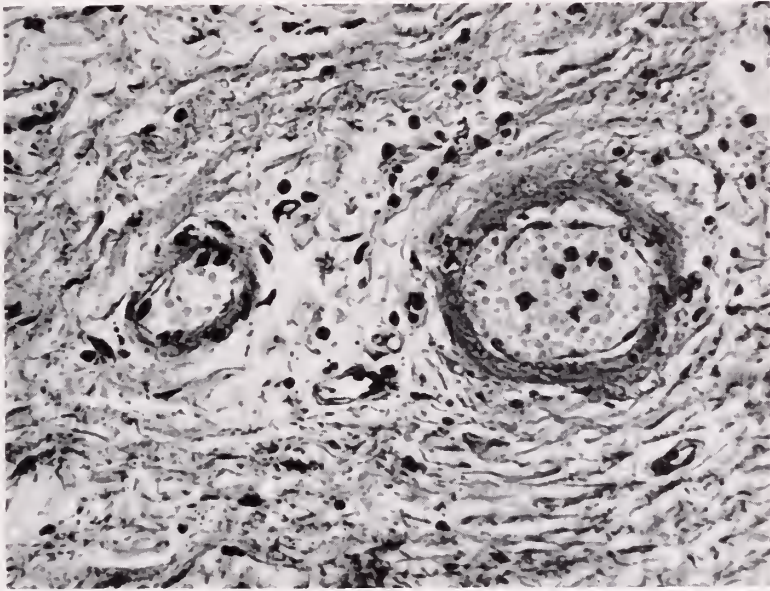


FIG. 1. Fibrinoid necrosis of small arteries in the wall of the stomach. Acute malignant hypertension and uremia in a dog due to great constriction of main renal arteries. (Hematoxylin-eosin,  $\times 440$ ). (Courtesy of Dr. H. Goldblatt)

of the myocardium (8). Fibrinoid necrosis of arterioles may also occur but is usually minimal (21) unless the life of the animal is prolonged by peritoneal lavage (8). In the acute and subacute experiments the distinction between the necrotizing arteritis and the smooth muscle necrosis was clear-cut (25). Morphologically, they differed in appearance and location and could be recognized even when they involved vessels of the same caliber, for example the main mesenteric artery. However, in certain chronic renal diseases, both arteritis and aortic media necrosis have been observed, for example, in antikidney serum nephritis (26, 27) and after three-fourths nephrectomy or after figure-of-8 ligature (28, 29). In antikidney serum nephritis the glomeruli and later the tubules become severely affected, causing interference with the circulation and tubular insufficiency. The same is true of three-fourths nephrectomy, which leads to eventual

fibrosis of the stump with gradual obliteration of glomeruli and loss of tubules (28).

Magarey examined the aortas of rats with long-standing hypertension and arteritis after constriction of one renal artery and removal of the opposite kidney (30). He observed focal cartilaginous metaplasia in some 15 per cent of 120 animals. These foci were mostly in the intima, where they appeared to follow hyalinization. They were also observed in the inner third of the media where they might have represented healed foci of muscle necrosis.

Both necrotizing arteritis and aortic medial necrosis are known to occur spontaneously in old rats (more than 500 days old). Either condition is usually associated with severe renal disease (which is considered to be pyelonephritis or nephrosclerosis (28, 31).

Administration of poorly soluble sulfonamides in the form of sodium salts causes obstruction of the collecting tubules in the kidney, damage to the collecting and convoluted tubules and temporary anuria or severe oliguria. Under these conditions a high proportion of rats develop hypertension and cytolytic necrosis of smooth muscle within a few days (32, 33). Although the vascular lesion is probably related to renal damage, some sort of direct action upon the smooth muscle cannot be excluded.

Medial necrosis with calcification occurs in the aorta and its major branches in choline-deficient rats. The vascular changes are preceded by severe renal disease characterized by hemorrhagic cortical necrosis with extensive tubular damage (34).

Hypertension and vascular lesions can be produced in the rat by administration of sodium chloride over a prolonged period of time (35, 36) particularly if it is accompanied by unilateral nephrectomy and the administration of steroids such as desoxycorticosterone (37), or by adrenal regeneration after enucleation (38). Vascular lesions are predominantly of the arteritis type, though fibrinoid necrosis of arterioles is also present (36, 38). In two animals killed in the 14th week of the experiment, Skelton (38) observed cartilaginous metaplasia in the aortic media. This might represent a sequel of previous medial necrosis. The renal lesions after administration of sodium chloride in any of the above experiments consist of glomerulonecrosis and subsequent fibrosis, dilatation of tubules and hyaline casts. Parabiosis accelerates the changes produced by sodium chloride (39). Hypertension caused by desoxycorticosterone may persist indefinitely after withdrawal of the drug (metacorticoid hypertension) (40). The vascular lesions in this type of hypertension are similar to those seen during the administration of desoxycorticosterone; in addition medial hypertrophy may develop.

Anterior pituitary hormones such as lyophilized anterior pituitary substance (41) or somatotrophic hormone (42) have been employed with results similar to those obtained from adrenal hormones. Wexler and Miller (43) reported that adrenocorticotrophic hormone given to old rats (old breeders) over one year old, caused severe necrosis and calcification of the vascular tree in the females, and necrotizing arteritis in the males. In this connection, it is interesting to note that

ACTH administered to bilaterally nephrectomized animals caused a rapid rise in blood pressure (44).

Acute segmental necrosis of small arteries (smooth muscle necrosis) has been produced by injection of sympathicomimetic amines (methoxamine) (45). These lesions are similar to those observed in dogs. Other vasoconstrictors such as vasopressin likewise caused arterial necrosis (46).

Administration of a massive dose of activated ergosterol or a diet rich in calcium, phosphorus or phosphoric acid produced coronary and aortic sclerosis, periarteritis nodosa, chronic nephritis and hypertension associated with widespread calcium precipitation (47). Large doses of parathyroid hormone (48), and likewise of thyroid hormone (thyroxin) (49) have a similar effect.

#### HYPERTENSION AND ARTERIAL LESIONS IN THE RABBIT

The rabbit has been studied less extensively than the rat, but available data indicate similarity of the vascular lesions in the two species.

Wilson and Pickering produced hypertension by the method of Goldblatt by constricting one renal artery together with contralateral nephrectomy or by constriction of both renal arteries (50). Vascular lesions observed in the animals two to four months later consisted of necrotizing arteritis and fibrinoid necrosis of the arterioles, mostly in the small intestine. In some arteries there was marked cellular intimal thickening with narrowing of the lumen. By and large the kidneys appeared normal both grossly and microscopically.

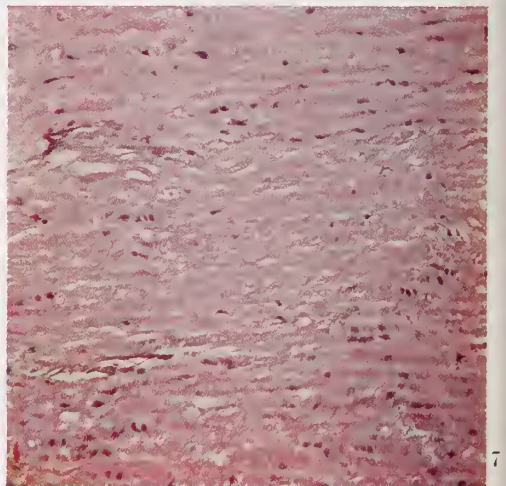
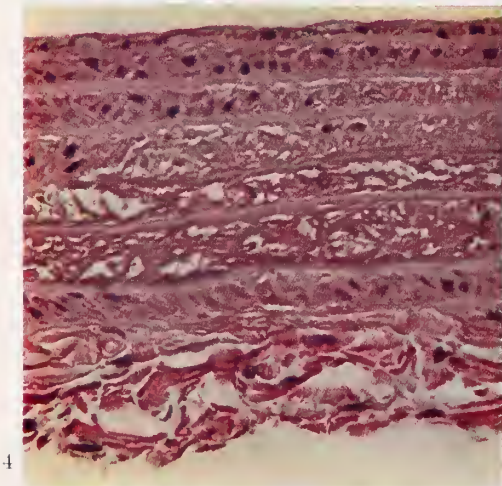
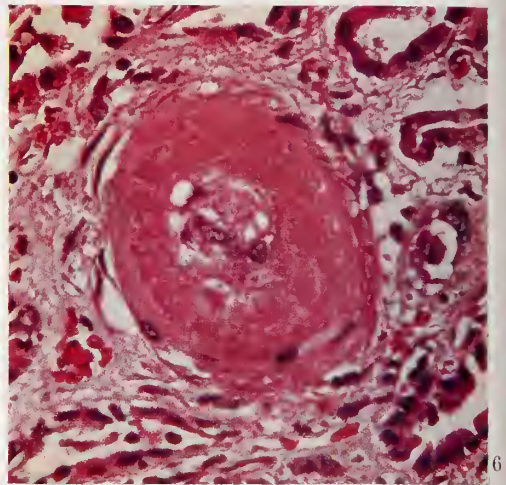
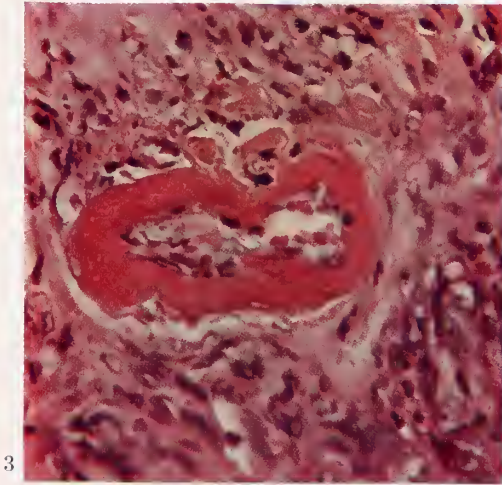
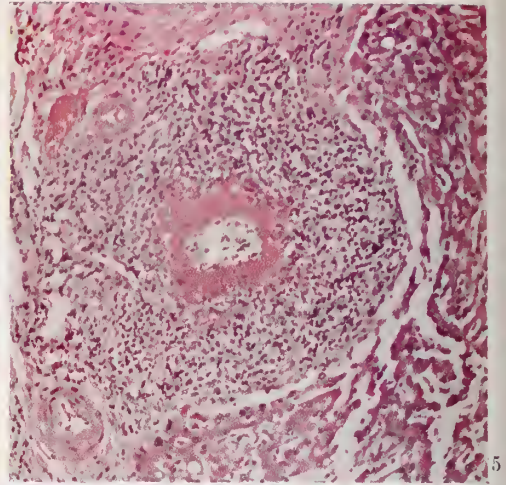
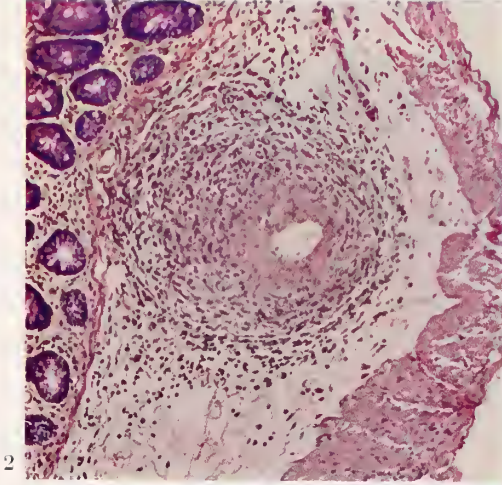
Campbell and Santos-Buch employed a different method, namely, the wrapping of one kidney in silk saturated in turpentine followed seven days later by contralateral nephrectomy (51). Vascular lesions similar to those observed by Wilson and Pickering were most prominent 22 days after wrapping of the kidney. In addition to those in the small intestine a few lesions were also seen in the heart, liver, gall bladder and testis. The appearance and distribution of the lesions differed from the vascular lesions obtained by injection of foreign protein. The occurrence of the latter lesions was not accompanied by elevation of blood pressure.

Unilateral pyelonephritis and ablation of the opposite kidney leads to hypertension and uremia associated with fibrinoid necrosis of the small arteries in the intestine (52).

Aortic medial necrosis and calcification can be produced in the rabbit by a variety of chemical substances. Some of these chemicals are distinctly nephrotoxic such as uranium (53). Others are not primarily nephrotoxic but act directly upon the smooth muscle: these include adrenalin (54), adrenalin in combination with thyroxin (55), or propylthiouracil (55) and tyramine (56). Arteritis has been reported in rabbits receiving excessive doses of vitamin D (57). This was associated with widespread calcification in the kidney.

Antikidney serum (derived from ducks) produced acute necrotizing arteritis concurrently with acute glomerulonephritis. Vascular lesions were found mostly in the kidneys (58).







## PATHOLOGY

The principal vascular lesions in experimental hypertension are fibrinoid necrosis, arteritis and cytolytic necrosis of smooth muscle.

Fibrinoid necrosis is seen predominantly in arterioles and small muscular arteries (Figs. 1, 3). The media is swollen and assumes a smudgy eosinophilic appearance; individual muscle fibers can no longer be recognized. Fibrinoid necrosis is usually unaccompanied by inflammation, but occasionally an inflammatory response is seen around the involved blood vessel probably related to the rapidity of necrosis. Red blood cells may be found in the wall of the necrotic vessel. It is likely that fibrinoid contains necrotic muscle protein (59) and proteins derived from the circulating plasma (60). Healing takes place by fibrosis. Fibrinoid necrosis is encountered in the dog, rat and rabbit. According to Goldblatt, in addition to hypertension, renal insufficiency is necessary for its production (61).

In the acute stage, necrotizing arteritis resembling periarteritis nodosa is characterized by inflammatory infiltration, mostly mononuclear, of the adventitia, rapidly followed by fibroblastic proliferation, necrosis in the media and subendothelial deposit of homogeneous eosinophilic material (fibrinoid) (Fig. 2). Necrosis of the media and destruction of the elastica tend to be focal. Blood protein can be demonstrated in the fibrinoid. The presence of muscle protein is less certain. Healing begins with cellular proliferation in the adventitia and intima. The media may regenerate or become fibrosed. Aneurysms may account for grossly visible nodules. Thrombosis is not common.

The distinction between fibrinoid necrosis and arteritis may be difficult when the latter involves very small arteries, or the former is accompanied by inflammation. Arteritis tends to involve preferentially the vessels of the splanchnic area. Arteritis has been described mainly in the rat and rabbit. Some degree of renal damage is often observed with arteritis; however, renal insufficiency is not a prerequisite.

Cytolysis of smooth muscle occurs in the walls of large arteries, in veins and in the muscularis of hollow viscera. In the dog the cytolysis often is accompanied by hemorrhage. In the rat it is seen most clearly as a cytolytic change with pyknosis and dissolution of the nuclei and rapid disappearance of the cytoplasm

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*Figs. 2 to 4: Vascular lesions in rat*

FIG. 2. Acute necrotizing arteritis in the wall of the intestine, produced by silk-wrapping of kidneys. (Hematoxylin-eosin,  $\times 110$ ).

FIG. 3. Acute fibrinoid necrosis of arteriole in the wall of the intestine, produced by right nephrectomy and great constriction of the aorta above the origin of the left renal artery. (Hematoxylin-eosin,  $\times 440$ ) (Courtesy of Dr. H. Goldblatt).

FIG. 4. Medianecrosis (smooth muscle necrosis) in the aorta after bilateral nephrectomy. (Hematoxylin-eosin,  $\times 440$ ).

*Figs. 5 to 7: Vascular lesions in man*

FIG. 5. Small artery in the liver showing periarteritis nodosa, associated with hypertension. (Hematoxylin-eosin,  $\times 110$ ).

FIG. 6. Arteriolar necrosis in malignant nephrosclerosis. (Hematoxylin-eosin,  $\times 440$ ).

FIG. 7. Medianecrosis (smooth muscle necrosis) in the aorta in hypertension. (Hematoxylin-eosin,  $\times 160$ ).

(Fig. 4). There is no inflammation, but calcium deposition is seen early. Subsequent changes are folding of the elastica followed by disruption, deposition of ground substance and eventually, healing by formation of cartilage or bone (Fig. 8). Disruption of the elastica may predispose to the formation of aneurysms. Cytolysis of smooth muscle in the aorta of the rat is localized predominantly in the middle or inner third of the media.

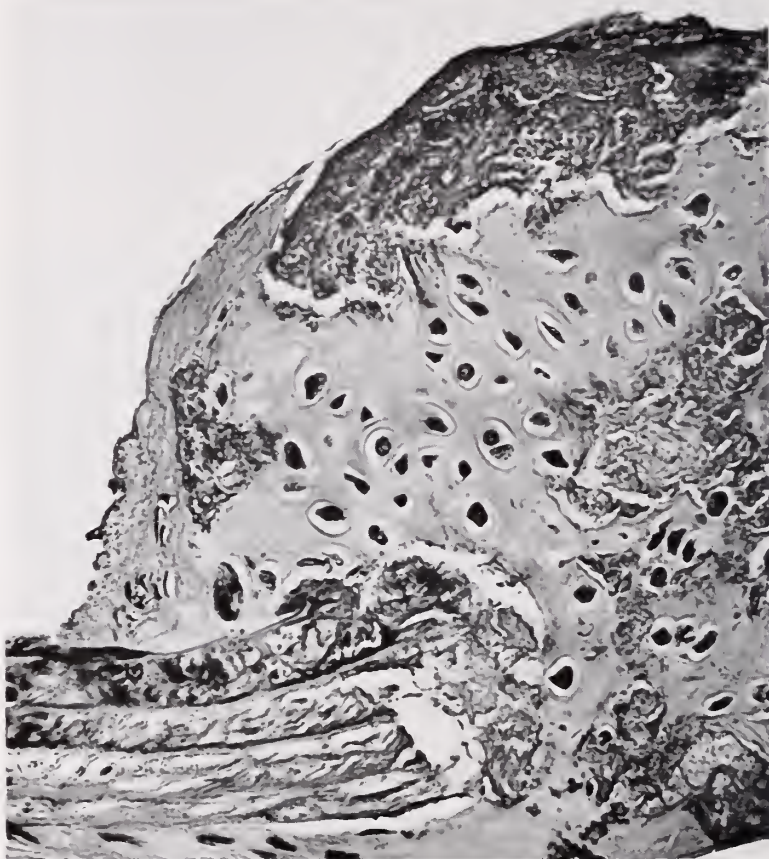


FIG. 8. Medianecrosis of the aorta and exuberant cartilaginous metaplasia in sulfonamide nephropathy in a rat. (Hematoxylin-eosin,  $\times 325$ ).

In chronic experiments in addition to sequelae of acute lesions, one may encounter medial hypertrophy of small arteries, intimal proliferation and focal medial degeneration, fibrosis and hyalinization.

#### RELATION OF VASCULAR LESIONS TO HYPERTENSION

Vascular lesions in experimental animals are usually though not invariably associated with hypertension. Hypertension may exist without vascular lesions of any consequence, and under some conditions lesions are observed in animals

with normal blood pressure; however, when the blood pressure is not elevated, lesions tend to be milder and less frequent. It is known that increased intravascular tension can damage the healthy vascular wall, but only when the latter is exposed to unusually forcible distention (62, 63). The range of pressure usually obtained in experimental hypertension is probably insufficient *per se* to cause significant damage to a normal vascular wall, but it will undoubtedly aggravate damage to an already weakened wall. In the final analysis, hypertension is caused by contraction of the smooth muscle especially that of the arterioles. The nature of the vasoconstriction or constrictors is not known in all instances and their mode of action is a subject for speculation. Necrosis of smooth muscle plays a large part in the development of vascular lesions. It may result from excessive and prolonged contraction, such as is seen after large doses of adrenalin. It has been suggested that in some types of experimental hypertension, such as those produced by renal infarction or by wrapping of the kidneys, two substances are elaborated; one is responsible for the elevation of blood pressure, the other for necrosis of the vascular wall (20, 64, 65). Some experiments suggest that different factors or a combination of factors are responsible for the production of hypertension, on the one hand, and of vascular lesions, on the other. To illustrate, renin alone will produce hypertension but no vascular lesions (66); when renin is combined with cortisone or DOCA, both hypertension and vascular lesions occur (66, 67). By contrast, vascular lesions without hypertension can be produced when a branch artery is ligated in adrenalectomized animals (21). Hypertension is, however, more elusive than are vascular lesions. Minor variations in blood pressure may not be considered significant, whereas even minimal vascular lesions can be recognized as manifestations of the underlying pathologic state.

#### ROLE OF THE KIDNEY

A two-fold relation exists between the kidney and the blood pressure. The kidney can *cause* hypertension when its hemodynamics are disturbed by such methods as constriction of the renal arteries, silk encapsulation or ligation of a branch artery. A normal intact kidney can also *protect* against development of hypertension. Renal hypertension is mediated by a humoral mechanism which is brought into play even if no structural or functional alterations can be observed in the affected kidney. This mechanism entails the secretion of renin and the formation of angiotensin (68, 69). Renin has been clearly demonstrated in the blood in the acute phase of experimental hypertension. Whether chronic hypertension is also mediated by renin has not been clearly established, although the beneficial effect of antirenin may testify to its presence (70). The mechanism of the protective action of the kidney is not known. Several possibilities have been suggested: (1) the normal kidney may inactivate hypertensive or angiotoxic substances produced by the diseased kidney; (2) it helps maintain water and electrolyte balance; and (3) it secretes into the circulation as yet unidentified substances concerned with the integrity of the vascular system. Combination of these or other factors now unsuspected may be operative (71-73). Removal of both kidneys causes hypertension (renoprival hypertension). This may be

explained by the loss of "protective action", with the stipulation that angiotoxic substances, if any, would be elaborated not in the kidney but elsewhere in the body.

The response to renal manipulations differs in various animal species. After manipulation of one kidney, the dog develops, as a rule, only transient hypertension, whereas the rat or the rabbit becomes permanently hypertensive. Similar differences exist with regard to the vascular lesions. In the dog, such lesions appear only if excretory renal insufficiency is present, or if both kidneys have been removed. In the rat or rabbit, some lesions, such as arteritis, are seen in an animal with one normal intact kidney. These observations suggest that both renal and renoprival mechanisms may be concerned with the vascular damage. In the dog, the latter mechanism is probably more important but a combination of both, such as might occur after bilateral ligation of the renal arteries, causes more severe damage. In the rat or the rabbit, several mechanisms may operate independently. Arteritis is probably caused by a substance elaborated in the diseased kidney and in that sense may be construed as a morphological equivalent of renal hypertension. Similarly, smooth muscle cytolysis may be interpreted as the counterpart of renoprival hypertension. The pathogenesis of fibrinoid arteriolar necrosis may also be related to a renoprival factor, or to both renal and renoprival factors.

#### ROLE OF ELECTROLYTES AND HORMONES

*Sodium:* Excess of sodium administered to rats over a prolonged period of time can induce hypertension and vascular lesions, mainly arteritis (35, 36). Extensive damage to renal parenchyma is usually, though not always, present at the same time (36). Sodium can also aggravate the hypertension of renal origin (24) and induce vascular lesions (74). However, the salt-free diet does not prevent the occurrence of vascular lesions although it reduces their incidence and ameliorates the hypertension (24). Renoprival hypertension in dogs is aggravated by salt-loading (75), but occurs also in the absence of exogenous excess of sodium (76). It is presumed that sodium acts by causing electrolyte imbalance in the tissues, although the nature of this imbalance is not clear. It has been suggested that it acts by lowering the potassium concentration in the muscle cells. This may lead to necrosis of the cardiac muscle but *per se* causes neither hypertension nor vascular lesions. However, recently Leonard has shown that decrease of potassium interferes with relaxation of the smooth muscle of the arterial wall (77).

*Adrenal cortical hormones,* notably those regulating electrolyte metabolism (mineralocorticoids) can produce hypertension and vascular lesions but only if sodium is supplied at the same time (37, 78). The changes develop more rapidly than on a high sodium diet alone, particularly if hormonal treatment is accompanied by unilateral nephrectomy. Under certain conditions (such as "cortical regeneration") the animal's own adrenal glands are capable of inducing hypertension and vascular disease either by direct action or *via* the kidney (38). Re-



removal of the adrenal glands, tends to lower established renal hypertension (21, 79), but does not interfere with the development of either hypertension or vascular disease of renal origin (80), though the latter tends to be milder and more sparse (21). The role of the adrenal cortex and sodium in renal hypertension appears to be more of a permissive or contributory rather than primary nature (81).

*Anterior pituitary hormones* such as somatotropic hormone affect the vascular system in a manner generally similar to that of mineralocorticoids. In addition, the presence of an intact pituitary gland enhances the action of the adrenal hormones (82). Hypertension caused by *adrenalin* is transient in nature but severe vascular lesions follow repeated administration, namely necrosis in acute experiments, and degeneration and calcification in chronic experiments. In contradistinction to the hormones of the adrenal cortex, the medullary hormone acts mainly upon the smooth muscle of the large arteries and on the arterioles. Vaso-pressin acts in a somewhat similar manner. Hormones of the *thyroid gland* enhance the action of adrenalin (55), and also that of mineralocorticoids (83).

Excess of *calcium* causes renal tubular damage, hypertension, calcification of the media of large arteries and smaller branches and also necrotizing arteritis (47). Administration of large doses of *vitamin D* or of *parathyroid hormone* has the same effect (47, 48). Calcification may be preceded by necrosis. It is not clear whether calcium acts directly or through the kidneys, or whether its role in renovascular disease is essential or permissive. Removal of the parathyroid glands inhibits, and administration of parathyroid hormone enhances, the cytolytic necrosis of smooth muscle following bilateral nephrectomy in the rat, but the same dose of hormone is ineffective in the presence of normal kidneys (84). Parathyroidectomy does not influence the development of arteritis caused by renal manipulations (85), nor of the fibrinoid necrosis of the arterioles in bilaterally nephrectomized dogs (86).

#### RENAL DISEASE, HYPERTENSION AND VASCULAR LESIONS IN MAN

Man differs from experimental animals in that he is subject to "essential" hypertension. Goldblatt pointed out the similarity between this type of hypertension, and renal hypertension in the dog (2). He postulated that essential hypertension in man is also of renal origin and is provoked by sclerosis and narrowing of renal arteries and arterioles. Evans suggested that sclerosis is the result of a congenital defect of renal arteries, namely, hypoplasia or aplasia of the media with secondary proliferation of the intima (87). Mosecowitz, among other students of hypertension, holds the opposite view that arteriosclerosis follows, rather than precedes the elevation of the blood pressure and that even normal blood pressure acting over a long period of time may cause arteriosclerosis (88). There is much evidence in favor of the first part of Goldblatt's thesis, with the reservation that sclerosis of renal arteries is not the only and perhaps even not the main eliciting factor, but that other stimuli may lead to malfunctioning of the renal mechanism concerned with blood pressure. The nature of such stim-



uli is unknown; some may be neurogenic in origin. In man, as in the rat or rabbit, persistent hypertension can be caused by unilateral renal disease.

The vascular lesions in human hypertension are similar to those observed in animals. Some of these are clearly related to the elevation of the blood pressure, although through what mechanism is speculative. Fibrinoid necrosis of arterioles (Fig. 6) accompanies malignant hypertension and sometimes chronic azotemic glomerulonephritis. In both conditions high blood pressure and renal insufficiency are present. Hypertension *per se* does not cause necrosis, although lowering of the pressure ameliorates it (89). On the basis of what has been said about

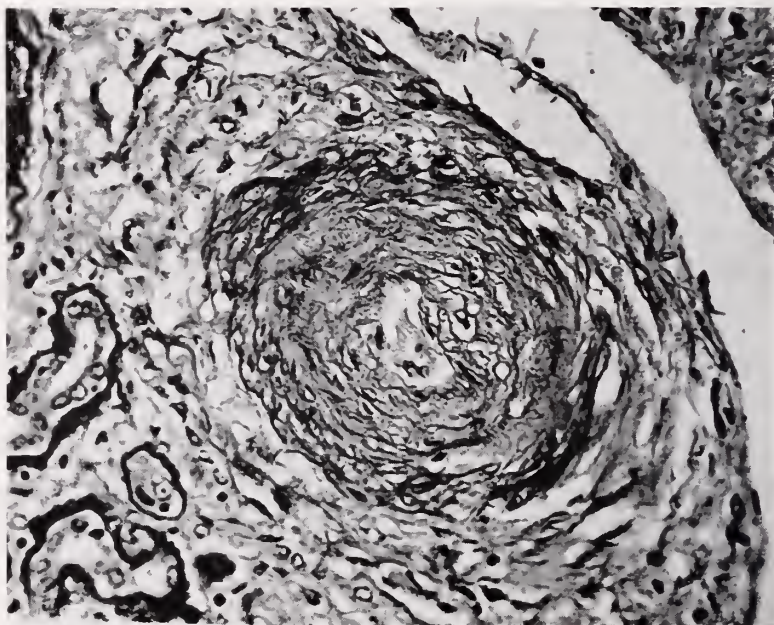


Fig. 9. Collagenous intimal hyperplasia ("onion peel") in an interlobular artery of the kidney in malignant nephrosclerosis in man. (Periodic acid-Schiff's reagent,  $\times 325$ ).

the dog, one may postulate that the "renoprival" factor plays a role in the development of these arteriolar lesions. The "onion peel" intimal thickening of arteries (90) (Fig. 9) is more conspicuous in the malignant hypertension of man than in that of the dog.

Necrotizing arteritis in man (Fig. 5) is frequently though not invariably accompanied and sometimes even preceded by hypertension (91, 92). The relationship between hypertension and diffuse vascular disease (periarteritis nodosa) in man has not been clarified, but there have been attempts to separate various forms of necrotizing arteritis on the basis of their presumed pathogenesis. Thus, Zeek distinguished between "hypersensitivity" or allergic arteritis and "true" periarteritis nodosa; the latter is frequently associated with hypertension and has its experimental counterpart in the necrotizing arteritis produced in the rat

by silk encapsulation of the kidneys (93). The recent work of Campbell and Santos-Buch appears to corroborate the "renal" origin of both the hypertension and the arteritis (51). By contrast, arteritis produced by foreign protein did not produce high blood pressure (51). It is possible that in some cases of periarteritis nodosa in man a "renal" mechanism plays an important role. This is probably true when periarteritis occurs in the course of chronic glomerulonephritis (94), and perhaps also when it follows, or develops concomitantly with "essential" hypertension.

Winternitz and Waters called attention to the fact that necrosis of smooth muscle fibers in the aortic media (Fig. 7) is not uncommon in malignant hypertension in man; its appearance is similar to that seen in the experimental dog (3). Gore and Seiwert pointed out that human medianecrosis occurs in two forms (95). In one, the damage begins in the elastic tissue, the patients are usually young, and have no hypertension, but frequently show various congenital defects, e.g. Marfan's syndrome. In the second form, the patients are middle-aged or old, show few if any congenital defects, but have hypertension in 85 per cent of the cases. A third intermediate form is also seen. As Gore emphasized, hypertension undoubtedly aggravates medianecrosis by increasing the burden placed upon the aortic wall. One may speculate, however, that here again hypertension and necrosis of smooth muscle have a common or closely related pathogenesis.

Elevation of blood pressure is often seen in endocrine disorders, particularly those of the adrenal gland, but vascular lesions are infrequent. Fibrinoid necrosis of small arteries and arterioles has been reported in rare instances of pheochromocytoma (96) and in Cushing's disease (97); in the latter, they are part of the syndrome of malignant hypertension. Administration of corticosteroids to patients with rheumatoid arthritis may be followed by necrotizing arteritis (98). Secretion of aldosterone is known to be increased in malignant hypertension. Recent studies indicate that this occurs in response to circulating angiotensin and is probably a sequel rather than the cause of hypertension (99).

#### SUMMARY

1. Published data on vascular lesions accompanying experimental hypertension are reviewed.

2. Acute vascular lesions such as necrotizing arteritis of medium-sized arteries, fibrinoid necrosis of arterioles and smooth muscle necrosis in the walls of large arteries are most easily produced by various renal manipulations, but also by administration of electrolytes and hormones. Chronic lesions either consist of healed necrosis or are represented by medial hypertrophy, degeneration, hyalinization and intimal proliferation.

3. In a susceptible animal such as the rat, interference with the circulation of the blood of even one kidney may cause a permanent rise in blood pressure and the appearance of arteritis. Similar changes can be produced by excess of sodium and by adrenal cortical hormones (mineralocorticoids).

Bilateral nephrectomy in the rat causes hypertension and cytolytic necrosis of smooth muscle. Severe tubular damage, excess of calcium or vitamin D and

large doses of parathyroid hormone or sympathicomimetic amines have a similar effect.

When renal insufficiency of any origin is present, fibrinoid necrosis of arterioles may be observed. Sympathicomimetic amines also cause necrosis of arterioles.

4. In a more resistant animal such as the dog, hypertension occurs only when both kidneys are interfered with. Vascular lesions do not develop unless renal insufficiency is present or both kidneys are removed. The lesions consist mainly of fibrinoid necrosis of arterioles.

5. Man is probably more susceptible than the dog but less susceptible than the rat. Hypertension occurs in unilateral renal disease, but acute vascular lesions (fibrinoid necrosis) usually require the presence of renal insufficiency. However, there are indications that some cases of necrotizing arteritis (periarteritis nodosa) may be causally related to the pre-existing or concomitant hypertension. Likewise, hypertension and some forms of medianecrosis of large arteries (smooth muscle necrosis) may have a common pathogenesis.

6. Electrolytes and hormones play an important role in the development of experimental hypertension and vascular lesions. It is not clearly established whether they all act upon the blood vessels directly or through the kidney. At the present time their role in human disease appears to be mainly permissive and contributory rather than primary.

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## THE CLINICAL EVALUATION AND MANAGEMENT OF THE HYPERTENSIVE PATIENT

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The hypertensive patient is frequently informed of his illness during the course of a medical examination when the initial finding of an elevated blood pressure is usually unsuspected. It is rare for a patient to come to a physician complaining of hypertension unless he has already been told of his disease by another physician. It is, therefore, clear that most cases of hypertension, at least initially, are asymptomatic and that many patients develop symptoms only after they know that they have hypertension. These early symptoms are variable and are generally similar to those of anxiety. They include palpitations, pounding sensations in the chest, headaches which are usually occipital, tremor, nausea and constipation or diarrhea (1). Furthermore, many unrelated intercurrent illnesses such as sinusitis, visual defects, constipation, labyrinthitis and even glaucoma may complicate hypertension and the symptoms indigenous to these conditions, especially headache and dizziness, may be erroneously attributed to the hypertension (2).

The hypertension itself may be symptom producing, although it is not unusual to see patients with blood pressures persistently above 200/110 who have no symptoms at all. The symptoms produced by the hypertension are usually caused by involvement of the so-called target organs, the most important of which are the brain, heart, eye and kidney (3).

In the brain, every gradation of clinical effect may be observed from the true hypertensive headache which is usually of a bursting type, often vertical in location, to full-blown hypertensive encephalopathy with stupor and even coma. In the retina, similar gradations can be observed from simple vasospasm to hemorrhages, exudates and papilledema (4). The cerebral and retinal manifestations, however, are not always parallel.

The most frequent effect of hypertension on the heart is hypertrophy. This is followed by left ventricular failure with attacks of nocturnal dyspnea and pulmonary edema (5). In the kidney, a progressive decrease in the glomerular filtration rate, renal blood flow and filtration fraction is the rule. An increased sodium diuresis after salt loading is a common finding, the nature of which is obscure. The earliest renal symptom is nocturia which is frequently accompanied by albuminuria and later isosthenuria and nitrogen retention (6, 7).

It is difficult to distinguish the signs and symptoms of hypertension associated with small blood vessel involvement from those of the complications of hypertension. If only one target organ were involved, the task would be easy; but the four target organs are often simultaneously involved at different rates. Further-

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Supported by grants from the American Heart Association and the National Heart Institute (H-1164, H-A-4477).

more, there are interactions among the kidney, heart and brain which complicate every manifestation. Thus uremia may complicate encephalopathy and heart failure may complicate renal failure, for example. In addition, large vessel arteriosclerosis is accelerated by hypertension and may complicate the entire disease process by such catastrophic events as coronary occlusion, peripheral vascular occlusion, cerebral hemorrhage or cerebrovascular thrombosis, berry aneurysm with hemorrhage, arteriosclerotic aneurysm with hemorrhage and dissecting aneurysm (8). Accompanying these conditions which are relatively indigenous to hypertension, there may be one or more unrelated intercurrent diseases such as a neoplasm, or infection which at any time may modify the hypertensive process. It can thus be readily understood why no two patients with hypertension are alike.

How can it be determined that the blood pressure is abnormally high in any given patient and that one is actually dealing with hypertension? In other words, where is the line drawn between a normal and hypertensive blood pressure? This problem is essentially one of clinical evaluation and, although normal standards that are correlated with age, sex and other factors are available, they are often unreliable because the normal groups may include large numbers of asymptomatic hypertensive subjects (9, 10). There is a need for a more reliable test for hypertensive disease than the blood pressure determination, and such tests as the cold pressor test, amytal test, digital vascular reactivity to norepinephrine test and others are available and may eventually find wider use. Meanwhile, it becomes the physician's responsibility to determine (A) whether a given patient's blood pressure is abnormally high and (B) whether this elevation indicates a need for treatment. It is clear that many factors such as anxiety, obesity and age must be considered in the clinical evaluation and that reliance on a single blood pressure reading is unwise.

It is apparent, therefore, that a careful history and physical examination including funduscopy is essential for the evaluation of hypertension. Blood pressures are best measured in the standing and recumbent positions and should also be measured in the lower extremities if there is any indication of coarctation of the aorta.

Routine laboratory tests including a complete blood count, urinalysis, sedimentation rate, blood urea, sugar and serum cholesterol determinations, are mandatory and in most patients, an electrocardiogram and chest x-ray are desirable. Other studies are then performed when clinical indications appear.

These simple clinical procedures are usually sufficient to differentiate most cases of primary or essential hypertension from secondary hypertension. Acute glomerulonephritis, for example, is usually diagnosed from the history, physical examination and urinalysis (11). Occasionally, however, essential hypertension with acute left ventricular failure can be confused with acute glomerulonephritis. Coarctation of the aorta and polycystic kidneys are usually identified by physical examination alone. A few cases require additional investigation, frequently of a simple nature but at times more complex, to determine the nature of the presenting hypertension.

In Cushing's syndrome, the habitus of the patient, the presence of a buffalo



hump, purple abdominal striae and osteoporosis will usually indicate the etiology of the hypertension and this can be confirmed by appropriate studies of steroids in the blood and urine and, perhaps, x-ray visualization of an adrenal tumor where this is present (12). In aldosteronism, primary or secondary, the differentiation is often more difficult. The cardinal manifestations of hyperaldosteronism in addition to hypertension are alkalinity of the urine and hypokalemia. The hypokalemia, however, may require several determinations for its detection. Interestingly, diuretics such as chlorothiazide can produce hypokalemia and if the urine is alkaline, this can be confusing. The diagnosis ultimately rests on the determination of aldosterone or its derivatives in the blood and urine and the methods available are still complex and imperfect. Even if aldosteronism is proved, it must still be determined whether it is primary or secondary, since many patients with essential hypertension may develop secondary aldosteronism late in the course of the disease. In either case, it must be decided whether therapy is to be medical using aldosterone inhibitors such as the spironolactones, or surgical.

The diagnosis of pheochromocytoma should be suspected in all patients with hypertension, although there are several features which should increase the index of suspicion. Some of these are: (1) onset of hypertension at a young age; (2) paroxysmal hypertension; (3) hypermetabolism; (4) decreased glucose tolerance and (5) tremor, sweating, etc. (13). Unfortunately, many of these manifestations may be associated with essential hypertension or anxiety and patients with pheochromocytoma may have fixed hypertension indistinguishable from essential hypertension. Pharmacologic tests with phentolamine or piperoxan if the blood pressure is elevated above 150/90 or the provocative test with histamine if the blood pressure is below this level are helpful. The definitive test for pheochromocytoma is the determination of vanillyl mandelic acid (VMA), the ultimate metabolite of the catecholamines in the urine (14-16). The catecholamines themselves may also be measured in the blood or urine. If the results are positive, an attempt to localize the tumor by x-ray after retrorectal air insufflation may be indicated.

The most difficult and troublesome problem, however, is the differentiation of chronic renal disease from essential hypertension (17-19). This is not always difficult since there are many cases of polycystic kidneys with moderate hypertension which are easily differentiated. Some cases of chronic glomerulonephritis are also easily identified, especially those of rapid progression, where the disease has been documented from its onset to the patient's death, and the clinical picture is dominated by renal failure and anemia with the hypertension as a mild associated feature of little clinical importance. A similar clinical course is observed in some cases of amyloid contracted kidneys and chronic pyelonephritis. The most difficult cases to interpret, however, are those in which the etiology of the hypertension is mixed; sometimes every diagnostic aid is required to establish the various etiological factors in these cases. Notwithstanding these additional examinations, and occasionally even at autopsy, it may not be possible to identify all of the factors involved.

The difficulty lies in the inherent complexity of chronic diseases involving the



cardiovascular and renal systems. Essential hypertension may produce nephrosclerosis which may predispose to pyelonephritis; whereas pyelonephritis, glomerulonephritis and diabetic glomerulosclerosis may produce hypertensive cardiovascular disease with resultant nephrosclerosis. In addition, the incidence of these diseases is such that adventitious coexistence is not uncommon. There is also reason to believe that the coexistence of these diseases with essential hypertension may alter the course of the hypertensive disease. Thus chronic glomerulonephritis in a patient with essential hypertension may produce an unusually accelerated malignant type of hypertensive vascular disease. This is exemplified in the diabetic patient where the diabetic nephropathy, *i.e.*, glomerulosclerosis or pyelonephritis, may exacerbate an underlying "essential" hypertension. If one considers the factor of secondary aldosteronism the end result becomes even more complex. An additional complication which has recently been discovered, is obstruction of the renal artery producing a Goldblatt kidney with hypertension. This may produce hypertension *de novo* but this sequence of events may also complicate essential hypertension.

What methods are available to distinguish these various factors in a patient with hypertension? If the clinical history, physical findings and routine laboratory investigations are suggestive of renal disease, further studies are in order. These include a timed intravenous pyelogram (1 min., 3 min., 5 min., 10 min. and 20 min.), routine test of renal function such as creatinine clearance, blood urea nitrogen, urine concentration test, phenolsulfonphthalein test, and a Howard test if a discrepancy between the two kidneys is suspected. An aortorenogram is indicated for definitive identification of renal artery obstruction. Renal biopsy is occasionally invaluable, although it is often of academic interest only and urine cultures present difficulties in interpretation because of urethral and bladder contamination, especially in females (20). Essential hypertension, moreover, can be identified by reactivity of the digital vascular bed to norepinephrine or angiotensin II, by the height of the blood pressure and its fluctuation, by funduscopy and by the cold pressor and amytal tests (21-26). From a therapeutic viewpoint, however, it is important to identify aortic or renal arterial obstruction which can be corrected surgically. When there is doubt as to the etiology of the hypertension, a therapeutic trial with antihypertensive drugs is indicated. Similarly, it may be important to identify the factor of hyperaldosteronism in a patient resistant to control.

Some patients with hypertension present themselves with one or more of the complications of the disease. These must be diagnosed and evaluated in terms of their interrelationship with the hypertension before therapy is decided upon. Such complications are hypertensive encephalopathy, uremia, coronary occlusion, coronary insufficiency, cerebrovascular accident, recent or old peripheral vascular thrombosis and congestive heart failure. A blood urea nitrogen greater than 60 mg per cent, an acute coronary occlusion or a cerebrovascular accident, is generally a contraindication to aggressive antihypertensive therapy. There are exceptions to this rule, however, especially where the blood pressure is dangerously high, but even here therapy should be instituted with caution. Angina

pectoris and coronary insufficiency may or may not be improved by treatment. Hypertensive encephalopathy or congestive heart failure, on the other hand, are usually indications for vigorous antihypertensive treatment if the blood pressure is high.

It is obvious that treatment will depend not only on diagnosis of the complications of hypertension, but also on identification of the underlying causes of the hypertension or of the associated diseases. If there is an adrenal cortical or medullary tumor, the treatment is surgical. If there is adrenal cortical hyperplasia, on the other hand, it becomes important to distinguish primary from secondary steroid hypertension and to decide whether therapy should be medical or surgical.

If obstruction to a large renal artery is found, the best procedure is surgical by-pass of the obstruction. In some instances nephrectomy will be necessary for technical reasons. If Goldblatt hypertension and essential hypertension coexist, antihypertensive therapy may still be necessary after surgery (27-30). In some cases, surgery may be contraindicated because of the age of the patient or associated renal failure or heart disease. Antihypertensive drug therapy should not be withheld in these instances.

If there is renal infection, treatment with antibiotics is indicated although it must be recognized that this is often unsuccessful. There is no specific therapy, of course, for loss of functional renal tissue, especially in chronic glomerulonephritis. In these cases therapy must await the development of renal transplantation procedures.

Drug therapy is the treatment of choice today for patients with essential hypertension and such therapy must also be given a clinical trial even if the hypertension is thought to be secondary to renal disease (31-35). This should be done especially if the blood pressure is inordinately high and if testing indicates that the factor of essential hypertension is present. The details of treatment with drugs are discussed elsewhere in this symposium. Sympathectomy is reserved for patients who cannot tolerate drug treatment or who do not cooperate in management with drugs. Adrenalectomy, although indicated in established primary steroid hypertension, has little rationale in essential hypertension and should still be considered an experimental procedure.

It is beyond the scope of this discussion to consider the management of all the complications of hypertension such as renal failure, vascular occlusion or congestive heart failure. These conditions are usually treated in the customary fashion without regard to the hypertension. When coronary occlusion decreases blood pressure, antihypertensive therapy is usually unnecessary but when the blood pressure is increased as in paroxysmal left ventricular failure, antihypertensive drugs may be important adjuvants to therapy.

#### SUMMARY

The incidence, onset and symptomatology of hypertension is discussed. The various factors which can elevate blood pressure in the hypertensive subject and their identification clinically have been considered. These include adrenal corti-

cal or medullary tumors and adrenal cortical hyperplasia with either Cushing's syndrome or aldosteronism; obstruction of the renal artery; intrinsic renal disease, such as glomerulonephritis or polycystic kidneys; coarctation of the aorta and essential hypertension itself. The management of these various types of hypertension occurring singly or in combination has been discussed; the occurrence and treatment of the complications of hypertension have been analyzed.

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## RENAL DISEASE WITH ASSOCIATED HYPERTENSION

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### INTRODUCTION

The association of renal disease and arterial hypertension was inferred by Richard Bright when he noted cardiac hypertrophy in cases with renal disease. He speculated that "greater action was necessary to force blood through the distant subdivisions of the vascular system" (1). In the latter half of the nineteenth century, despite the cumbersome methods available for measuring blood pressure, reports began to appear describing hypertension in association with renal disease (2, 3). With the advent of the pneumatic cuff at the beginning of the twentieth century, the recognition of high blood pressure in patients with renal disease became more frequent. This association led investigators to propose that all hypertension was of renal origin. However, it was not long before the concept of essential hypertension as a distinct clinical entity, was introduced, and a renal origin for hypertension was discarded (4-6). More recently, the experiments of Goldblatt have produced a resurgence of interest in the kidney and its role in the production of hypertension (7). While the present review will deal chiefly with the hypertension associated with primary intrinsic disease of the kidney, it appears appropriate to summarize briefly the experimental and clinical data relating the kidneys and hypertension in the absence of intrinsic renal disease. Hypothetical alterations of kidney function that have been implicated in relation to nonspecific hypertension include the following:

#### *1. Failure of the kidney to destroy or excrete a pressor substance*

Hypertension may or may not be present in uremia. In acute glomerulonephritis with anuria, hypertension is common; in acute tubular necrosis with anuria, conspicuous hypertension is infrequent. Grollman found that hypertension occurred in bilaterally nephrectomized dogs. When the animal was kept alive with hemodialysis, so that the blood urea nitrogen concentration remained normal, the hypertension persisted (8). Muirhead *et al.* showed that a functioning renal homograft reduced the blood pressure to normal in a nephrectomized dog (9). These findings suggest that the failure of urinary excretion of a pressor substance is probably not the sole factor in the production of the hypertension, but that a metabolic activity of the normal kidney may inactivate a pressor substance.

#### *2. Failure of the kidney to form and secrete an antipressor substance*

The consistent production of hypertension in bilaterally nephrectomized dogs and rats suggested to some that the kidneys may liberate some antipressor sub-

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stance into the blood stream (8, 10). Hamilton and Grollman demonstrated amelioration of renal hypertension in rats when they were given a purified extract of kidney (11). However, no purified fraction of kidney has been demonstrated to lower blood pressure consistently in experimental animals or man.

### 3. *Production by the kidney of a vasoconstrictor*

In 1898, Tigersted and Bergman produced elevation of the blood pressure in the dog by intravenous administration of saline extracts of kidney; similar results were obtained by the administration of renal vein blood. They suggested the presence of a pressor substance which was termed renin (12). This work was forgotten until, following Goldblatt's experiments in 1934 (7), investigations were again started with kidney extracts, and renin was rediscovered (13). Braun-Menendez and Page and Helmer, independently, concluded that renin was an enzyme that acted on a substrate in the plasma to produce a vasoconstrictor substance termed hypertensin (angiotonin) (14, 15). Subsequently, many workers have reported increased quantities of renin and, or hypertensin in animals with experimentally produced hypertension and in hypertensive patients. Quinby demonstrated the presence of renin in homolateral renal venous blood in man after constriction of the renal artery (16). Kahn *et al.* found a concentration of hypertensin in the blood of patients with malignant hypertension twenty times that observed in normal subjects (17). Skeggs *et al.* reported increased blood concentrations of hypertensin in dogs made hypertensive by renal artery obstruction (18). However, a number of negative reports have likewise appeared. Several groups have noted that the renin content of the kidney increased during the first few months of hypertension produced by renal artery obstruction, but that the quantity decreased thereafter despite persistence of the hypertension (19, 20). Peart could not demonstrate an increase in renin or hypertensin in samples of renal vein blood from 26 severely hypertensive patients with and without intrinsic renal disease (21). The administration of sufficient hypertensin to cause hypertension in normal patients produced a reduction of skin blood flow, as contrasted to the normal skin blood flow recorded in most spontaneous forms of hypertension. Furthermore, normal patients given hypertensin with resulting hypertension, showed reduced rates of urine flow and electrolyte excretion. Administration of hypertensin to patients with severe hypertension and renal disease, producing a further rise in the blood pressure, caused an increase in urine flow and electrolyte excretion. These workers, therefore, concluded that the renin-hypertensin system did not appear to be involved in the varied types of clinical hypertension studied (21).

### 4. *Effect of the kidneys on electrolyte and water balance*

A change in the normal distribution of body water and electrolytes has been implicated in the etiology of hypertensive disease. Eichelberger suggested that an increased intracellular sodium concentration occurred in hypertension (22). Diets containing considerable quantities of hypertonic salt produced hyperten-

sion in the rat (23), ostensibly by causing increased arterial wall salt content, swelling of the arterial wall and a subsequent reduction of the lumen of the vessels. Ross reported an elevated total exchangeable sodium, and Grollman an increased extracellular volume in hypertensive subjects (24, 25), but this finding could not be substantiated by Moore *et al.* (26). It has been demonstrated that the hypertensive patient handles a salt load differently from the normotensive patient; that is, he excretes a greater proportion of the administered salt load (27). White showed in the dog that excretion of salt and water was directly proportional to the pressure in the renal artery, i.e., a rise in intrarenal arterial pressure caused an increased rate of sodium and water excretion, but that lowering the renal artery pressure decreased the rate of sodium and water excretion (28). It is now generally believed that whatever the abnormality of electrolyte

TABLE I

*Renal Disease with Associated Hypertension**A. Intrinsic Diseases of the Kidney*

- 1) Glomerulonephritis, acute and chronic
- 2) Chronic Pyelonephritis, bilateral and unilateral
- 3) Polycystic Kidney Disease
- 4) Unilateral Renal Artery Disease
- 5) Radiation Nephritis
- 6) Toxemia of Pregnancy\*
- 7) Renal Amyloidosis

*B. Systemic Diseases with Renal Involvement*

- 1) Polyarteritis Nodosa and related "acute necrotizing arteritides"
- 2) Systemic Lupus Erythematosus
- 3) Scleroderma
- 4) Diabetic Glomerulosclerosis

\* Discussed elsewhere in Symposium.

metabolism in the hypertensive patient, this alteration is probably secondary to the hypertension rather than a primary etiologic factor.

The purpose of this paper is to present the clinical characteristics of the hypertension associated with intrinsic diseases of the kidney, and to summarize diagnostic techniques and therapeutic management of this hypertension. Table I lists the primary renal diseases most frequently associated with hypertension. A number of systemic diseases of unknown etiology affect the renal vasculature secondarily and are associated with hypertension (Table I), but these are discussed only briefly.

## GLOMERULONEPHRITIS

Glomerulonephritis is a bilateral, nonsuppurative, inflammatory disease of the kidneys, which may appear in an acute or chronic form. The clinical course is characterized by proteinuria, edema, hematuria, renal insufficiency and hypertension.

*Acute Glomerulonephritis*

Acute glomerulonephritis appears predominately as a disease of childhood and young adult life. Seegal *et al.* reported 50 per cent occurring before the age of 10 years and 70 per cent of cases before the age of 21 years (29). Fishberg stated that the occurrence of acute glomerulonephritis is "rare in the aged", but the recognition of this disease in patients past the fourth decade of life is occurring with increasing frequency (30, 31). Instances of this disease in subjects in the seventh or eighth decade of life are not uncommon. Hypertension occurs in 50 to 80 per cent of patients with acute glomerulonephritis (32-34). The elevation of blood pressure is seen in both the systolic and diastolic readings. The rise may be sudden and the fall just as precipitous, with the readings in any one day fluctuating over a wide range. The duration of the hypertension is variable, but it usually begins to fall within one week of its onset. While the severity of the hypertension cannot be correlated with the prognosis, it can be associated with cerebral symptoms such as headache, drowsiness, vomiting and convulsions (hypertensive encephalopathy). Hypertensive crises are more common in the child than in the adult.

The mechanism for the production of the hypertension in acute glomerulonephritis is unknown. Many investigators consider it to be related to renal ischemia produced by the renal lesion. Pickering quotes the paper of Mahomed (3), in which the observation is made that the hypertension may precede the proteinuria, to suggest that the hypertension may not be due to the renal lesion (35). Pickering suggested that the hypertension may result from a generalized allergic vascular reaction as a direct consequence of edema of the blood vessel walls and generalized vasoconstriction. However, in other studies, it has been suggested that a primary generalized vasculitis does not underlie the hypertension (36). The severity of the hypertension is often dependent on the degree of salt retention, but the basis of this relation is not understood.

Renal function studies do not elucidate the pathogenesis of the hypertension. Earle, Taggart and Shannon found that in patients with acute glomerulonephritis, the glomerular filtration rate ( $C_F$ ) was decreased early, while the tubular maximal excretion of diodrast ( $Tm_D$ ) was less affected (37). The reduced  $C_F/Tm_D$  ratio demonstrated that the major effect of the disease was on the glomerulus. The reduction of the  $C_F/Tm_D$  ratio was the same in nephritic subjects with or without hypertension. The hypertension was, therefore, ineffective in increasing either the glomerular filtration rate or the renal plasma flow. Bradley *et al.* observed that both the glomerular filtration rate and effective renal plasma flow were reduced in acute nephritis, but the latter to a lesser extent (38). Similarly, the maximal tubular excretion of PAH ( $Tm_{PAH}$ ) and the extraction of PAH ( $E_{PAH}$ ) were reduced, suggesting some perfusion of damaged tubular tissue. The renal blood flow, calculated as renal plasma flow/PAH extraction ratio  $\times$  1-hematocrit, was normal in 8 out of 9 subjects, indicating the presence of renal hyperemia.

Clinically, the severity and complications from the hypertension are often correlated with the degree of salt retention. Consequently, if salt restriction

is not instituted early in the course of the disease, the cardiac and cerebral manifestations of fluid accumulation often dominate the clinical picture. In most instances, the threat produced by the increased systemic pressure subsides coincident with the development of a salt diuresis. The awareness of the importance of bed rest and fluid and salt restriction in preventing further salt retention and initiating a spontaneous salt diuresis has, therefore, proved to be the most effective measure for treating the hypertension and its sequelae. For this reason, judicious diuretic therapy may offer a most valuable adjunct in the treatment of the hypertension. The indications for the use of antihypertensive therapy in acute glomerulonephritis are not explicit. Skepticism has been raised as to the value of lowering asymptomatic hypertension (39). In addition, some of the antihypertensive drugs have been shown to have a deleterious effect on renal hemodynamics (40-42). In recent years, the trend has led away from the use of potent hypotensive agents except in preventing or treating hypertensive crises. While the severity of the hypertension can usually be correlated with hypertensive crises, there are exceptional cases in which encephalopathy is seen with only modest blood pressure elevations (43). Symptoms and signs, such as irritability, nausea, vomiting, headache, a rising pulse rate (bradycardia is often seen with hypertension in acute glomerulonephritis) and a sudden elevation of blood pressure, should alert the physician to the possibility of an impending episode. The development of hypertensive crises is infrequent in hospitalized patients in whom salt restriction and bed rest have been imposed.

### *Chronic Glomerulonephritis*

Chronic glomerulonephritis may follow acute glomerulonephritis (Ellis type I or Longcope type A), or its onset may be insidious without any preceding acute illness (Ellis type II or Longcope type B). Either type may be associated with hypertension. In the type occurring after acute glomerulonephritis, one of the following several courses may be seen:

- 1) intensification of the edema, hypertension and renal insufficiency, with uremia occurring within a few months to a year.
- 2) development of a nephrotic syndrome with edema, proteinuria, hypoproteinemia and hypercholesterolemia, occurring with or without hypertension.
- 3) recurrent acute attacks with edema, hematuria and hypertension. Following each attack evidence of increased renal insufficiency may be present.
- 4) a latent period of many years between the acute attack with little or no signs or symptoms except for modest proteinuria, but ultimately the development of renal insufficiency and hypertension.
- 5) the presence of hypertension as the major manifestation of chronic glomerulonephritis. Years later renal insufficiency may occur.

Likewise, the clinical picture seen in the chronic glomerulonephritis of insidious onset may vary considerably. The disease may present with a benign but persistent proteinuria, a nephrotic syndrome, frank renal failure, or primarily with hypertension. The majority of adult patients cannot recall a disease resembling acute glomerulonephritis, and therefore must be placed in this latter group.



Hypertension is a classical sign of chronic glomerulonephritis. Bell in a study of 167 cases of chronic glomerulonephritis found hypertension present in 153 cases (43). The severity and characteristics of the hypertension in chronic glomerulonephritis is usually related to the nature and severity of the renal disease. Early in the course, the hypertension is usually mild to moderate and is not as labile as that seen in essential hypertension. Bell found that the blood pressure tended to rise with increasing renal insufficiency (43). This finding was contrasted to the blood pressure observed in essential hypertension which is often quite high before the onset of renal failure. In those cases of chronic glomerulonephritis characterized by recurrent acute attacks, the blood pressure may rise with each exacerbation and be normal during remissions. When the disease is in a nephrotic phase, the elevated blood pressure may fall to normal levels. While the level of blood pressure tends to be lower than in essential hypertension, a course identical with the malignant phase of essential hypertension may occur (44).

The use of percutaneous renal biopsy has shown that many cases of asymptomatic hypertension detected during routine physical examination are associated with chronic glomerulonephritis. This hypertension is not accompanied by detectable signs of renal or cardiac failure. Its course is often as benign as that of essential hypertension, and may persist for many years before the sequelae of cardiac, cerebral or renal failure become evident. In most of these subjects, the hypertension represents the major expression of the underlying nephritis, with renal function being well preserved. The only hint of the occult renal disease may be the persistent proteinuria which is extremely rare in uncomplicated essential hypertension. When, after several decades, the glomerulonephritis progresses to renal failure, it may be difficult to differentiate the hypertension from that associated with malignant nephrosclerosis without nephritis.

The mechanism for the production of hypertension in chronic glomerulonephritis, as in acute glomerulonephritis, is unknown. While arteriolar sclerosis and endarteritis obliterans are often seen in the kidney of subjects with chronic glomerulonephritis, most observers feel that these lesions correlate with the presence of the hypertension and are not caused by the glomerulonephritis. Hogeman reported that glomerular filtration rate, renal plasma flow, filtration fraction and renal blood flow are reduced to a greater extent in chronic glomerulonephritis than in acute glomerulonephritis (45). The most marked depression in renal function was noted in those patients with a blood pressure greater than 190/100 and a nonprotein nitrogen greater than 40 mg per cent. Earle, Taggart, and Shannon found in patients with chronic glomerulonephritis that  $C_F$  and  $Tm_D$  fell as the disease progressed (37). However, in the latter stages, there appeared to be an acceleration of tubular loss, as demonstrated by a rise in the  $C_F/Tm_D$  ratio and a decrease in diodrast clearance. While hypertension in all cases could not be correlated with a reduction of functional renal tissue, diastolic hypertension was found more commonly with depressions of  $Tm_D$  greater than forty per cent of normal. The previously quoted pathologic, clinical and physiologic data indicate that hypertension does supervene in subjects with chronic glomerulonephritis as renal failure develops. However, it also has



become evident that subjects with proteinuria as the only manifestation of glomerulonephritis are vulnerable to superimposition of hypertensive disease which is not easily distinguishable from essential hypertension, and that this hypertensive disease may occur without the coincident development of renal failure.

The management of the hypertension associated with intrinsic renal disease is independent of the type of renal disease. The perpetuation of untreated hypertension will produce progressive nephrosclerosis which, when superimposed on the intrinsic renal disease, will further diminish the residual functioning renal parenchyma. Therefore, when the hypertension represents the most conspicuous manifestations of the clinical picture and renal function is relatively well preserved, such hypertension should be treated as in the subject without intrinsic renal disease. The potency of the agents to be employed, as in the subject with essential hypertension, will depend on the natural course of the hypertensive process. If the hypertension is severe and rapidly progressive, ganglionic blocking agents, diuretic therapy and even sympathectomy may have to be employed. It is important that the level of renal function be carefully scrutinized during the course of such treatment. Antihypertensive therapy in the subject with a considerable degree of renal failure poses a more difficult problem. In this group, the indiscriminate use of potent antihypertensive agents may lead to severe and irreversible renal failure. On the other hand, when congestive heart failure, hypertensive retinopathy and encephalopathy present life threatening complications, antihypertensive therapy may be used as a desperation measure.

#### CHRONIC PYELONEPHRITIS

Chronic pyelonephritis represents the most common form of intrinsic renal disease. Since 25 to 60 per cent of patients with chronic pyelonephritis have associated hypertension, pyelonephritis is the most common renal disease associated with hypertension (46, 47). Although chronic pyelonephritis is frequently noted at postmortem examination, the clinical diagnosis is often difficult and frequently missed (48-50). Kleeman, in a study of 629 cases found pyelonephritis unrecognized during the lifetime of 83 per cent of these subjects (51). The frequency with which the pyelonephritis is overlooked and the association of hypertension in a large number of such cases, suggest the possibility that many patients with hypertension of unknown etiology may have underlying pyelonephritis.

The incidence of hypertension in chronic pyelonephritis depends on whether atrophic or nonatrophic pyelonephritis is considered, the incidence being significantly higher in the former group. Hypertension in patients with bilateral atrophic pyelonephritis has been reported in 60 to 68 per cent of cases, while in non-atrophic pyelonephritis the incidence was one-third as frequent (47, 50, 51). The cause of this greater incidence in chronic atrophic pyelonephritis is not clear. Kleeman found no correlation between serum creatinine and hypertension, and concluded that the loss of renal mass did not explain the difference (51). In histologic examination of pyelonephritic kidneys, several investigators, noting certain vascular changes in the atrophic group, suggested that this may lead

to the development of the hypertension (47, 51, 52). Weiss and Parker demonstrated a relationship between the severity of the vascular lesions and the hypertension (47). They described a proliferative hyperplastic arteriosclerosis which they believed to be attributable to the inflammatory pyelonephritic process. This vascular lesion was seen chiefly in areas of pyelonephritic scarring and, in unilateral pyelonephritis, on the affected side. These authors concluded that these arteriolar lesions produced renal ischemia which caused the hypertension. Kincaid-Smith was able to correlate the severity of renal contraction and pyelonephritis with the presence of hypertension (52). Histologic studies revealed numerous lesions of incomplete infarction, called the "ischemic lesion". These lesions were not arterial but were parenchymal, and represented ischemic renal parenchyma that had escaped complete destruction. The conclusions of this study were that these "ischemic areas" were causally related to the hypertension. Despite the documented greater incidence of hypertension in chronic pyelonephritis, it must be remembered that a large number of cases with severe chronic pyelonephritis exist without hypertension. Histologic changes just as marked as those seen in patients with hypertension have been reported in subjects without hypertension. Longcope could find no correlation between the vascular lesion in pyelonephritis and the presence of hypertension (53).

Renal function studies performed in patients with chronic pyelonephritis do not elucidate the mechanism for the production of the hypertension. Raaschou found in 31 patients with chronic pyelonephritis, a reduction in renal plasma flow and tubular function with a relatively well preserved glomerular filtration rate, suggesting that the kidneys are ischemic (54). However, Brod, while admitting that the incidence and severity of the hypertension seemed to increase with progression of the disease, noted that twenty per cent of patients with chronic pyelonephritis and hypertension had normal or only slightly impaired renal function. He concluded that hypertension may occur in chronic pyelonephritis with barely demonstrable physiologic changes (48).

The clinical picture and the level of renal function at the time hypertension is discovered is quite variable. The hypertension may be severe with either no evidence of renal failure or with marked renal insufficiency. The hypertension may persist without any clinical evidence of active renal infection, and it may even advance to a malignant phase when the pyelonephritis is in a healed stage. The malignant phase of hypertension is not uncommon in chronic pyelonephritis. While an accelerated phase occurs in only two per cent of patients with essential hypertension (50), pyelonephritis is found in 15 to 21 per cent of cases of malignant hypertension (47, 48, 50, 51).

The insidious course of chronic pyelonephritis and its association with hypertension was emphasized by Saphir and Taylor who coined the term "pyelonephritis lenta" for those cases of chronic pyelonephritis that presented with hypertension and renal failure, but without overt evidence of infection (55). This group was composed of patients usually less than fifty years of age, with hypertension, anemia, proteinuria and a urinary sediment containing an in-

creased number of white blood cells. The kidneys were small and scarred. Uremia was precipitated in fifty per cent of such cases by an acute exacerbation of the underlying pyelonephritis.

It seems evident then, that, in the patient with hypertension of unknown etiology, the presence of pyelonephritis must be suspected. If there is a history of genitourinary tract infection in childhood, attacks of cystitis during pregnancy, a history of diabetes mellitus, or recurrent colic and dysuria, the diagnosis is not difficult. However, such a history is rarely obtained. Unfortunately, atrophic pyelonephritis, the form most commonly associated with hypertension, is most frequently asymptomatic. Certain laboratory tests may be of assistance in making the diagnosis of occult pyelonephritis. A flat film of the abdomen (KUB) may reveal small kidney shadows. Intravenous and retrograde pyelography may reveal the characteristic changes of pyelonephritis. Repeated examination of the urinary sediment usually reveals an increase in the number of white blood cells, although the diagnosis of pyelonephritis cannot be discarded because pyuria is absent. Proteinuria is usually only modest. Culture of the urine may reveal pathogenic organisms. Recent observations indicate that, with proper bacteriological techniques, bacteriuria can be quantitated and, by these methods, "significant" counts can be correlated with the presence of genitourinary infection (56). The urine specific gravity is often fixed at isosthenuric or even hyposthenuric levels despite meager degrees of renal insufficiency. It may be impossible to differentiate the hypertension associated with pyelonephritis from that occurring in chronic glomerulonephritis without the aid of renal biopsy. A 24 hour urinary protein excretion exceeding 2.5 Gm per day suggests that the glomerular lesion of nephritis is present, for such levels are rare in patients with pyelonephritis who are not diabetic, in severe congestive heart failure, or in the malignant phase of hypertension. With moderate to marked hypertension, the degree of renal failure may be comparable. The incidence of hypertension in chronic glomerulonephritis and pyelonephritis is almost the same. The similarity of clinical and laboratory findings in these two diseases led Brod to suggest that blood pressure is raised by the same mechanism in both (48).

Unilateral chronic pyelonephritis, as well as the bilateral disease, may be associated with hypertension. The clinical characteristics do not differ from those described for bilateral chronic pyelonephritis. The importance of the recognition of unilateral pyelonephritis rests on the fact that nephrectomy may occasionally lead to cure (57). Perera and Haelig suggested that when the hypertension appears for the first time in a patient less than fifty years of age and unilateral pyelonephritis is present, nephrectomy may be beneficial (58). However, it is unfortunate that the diagnosis of unilateral pyelonephritis is difficult to make with certainty. The reader is referred to the section dealing with unilateral renal artery disease for discussion of diagnostic techniques.

The treatment of hypertension in patients with bilateral pyelonephritis presents some problems quite similar to those noted in subjects in which the hypertension is associated with glomerulonephritis. Intensive treatment of such

patients should be undertaken only when the severity of the vascular disease presents the primary problem. As in patients with glomerulonephritis, vigorous therapy including ganglionic blocking agents and repeated treatment with diuretics, in the presence of moderate to marked renal failure, may accelerate renal failure with the evolution of an irreversible uremic syndrome. However, when the hypertension represents a life threatening complication with severe retinopathy, heart failure and even hypertensive encephalopathy, the physician may have to resort to potent antihypertensive therapy. As agents of increasing potency are added to the therapeutic regimen, renal function must be carefully watched because sudden deterioration may occur. For those subjects in whom the degree of hypertension is disproportionately greater than the reduction in renal function, the antihypertensive therapy may become more vigorous. In such patients ganglionic blocking agents, diuretics and even sympathectomy may be employed. Antihypertensive treatment in the absence of appreciable degrees of renal failure may be vital, because the vascular sequelae of long-standing hypertension will further diminish the remaining renal function. Throughout such therapy the level of renal function must be carefully followed. In subjects with accelerating hypertension in association with unilateral pyelonephritis and relatively well preserved total renal function, a nephrectomy may have to be performed. However, the frequency with which patients undergo a sustained cure is far less than subjects in whom the unilateral renal disease is consequent to unilateral vascular disease.

Clinical and experimental evidence demonstrate that acute exacerbation of the renal infection may intensify the hypertension and precipitate a uremic syndrome (55, 59). Active and vigorous antibiotic therapy is indicated with any sign of infection, or even with suspicion of its presence. Likewise, obstructing lesions of the lower urinary tract should be removed when possible.

#### POLYCYSTIC KIDNEY DISEASE

Polycystic kidneys occur as a heredofamilial maldevelopment in which both kidneys are usually affected, but unilateral involvement is not uncommon (60). This anomaly generally produces symptoms in infancy (infantile type) or after the third decade (adult type). One form of the infantile type is the unilateral multicystic kidney (61). This entity rarely causes symptoms and is usually discovered when a lobulated mass is felt in the flank of an apparently healthy infant. Hypertension, pain, fever and hematuria are rare.

Bilateral polycystic kidney disease may present with symptoms of abdominal pain, fever and hematuria (surgical type) or, with symptoms of renal insufficiency and/or hypertension (medical type), and more often, as a combination of both types. The presence of hypertension has been recorded in approximately 75 per cent of cases of polycystic kidney disease (60, 62). In one report of 180 cases, 139 showed hypertension in association with renal insufficiency, 10 revealed renal insufficiency without hypertension, and 27 cases showed no evidence of renal insufficiency or hypertension (63). From this study, it appears that there is some correlation between the degree of renal insufficiency and hy-



pertension. While this is the general rule, as in other forms of renal disease, hypertension may represent the most conspicuous feature of the clinical picture with relatively well preserved renal function.

The pathogenesis of the hypertension in polycystic kidney disease is unknown, but it has been related by some workers to the loss of renal parenchyma. Bell expressed the view that the renal ischemia produced by the cysts caused the hypertension (64), but there is little support for this hypothesis.

The clinical course of polycystic kidney disease is generally prolonged and characterized by many asymptomatic years, punctuated by exacerbations of fever, pain and hematuria. These patients may remain in apparent good health while there occurs an insidious, almost imperceptible progression of the renal failure. Generally, the hypertension, with its sequelae of cardiac enlargement, cerebrovascular accidents and heart failure, become superimposed as the renal failure progresses. The indications for treatment of the hypertension are identical with those discussed above under pyelonephritis.

#### UNILATERAL RENAL ARTERY DISEASE

The studies by Goldblatt in 1934, in which arterial hypertension was produced in the dog, stimulated widespread interest in the relation between unilateral renal vascular disease and hypertension (7). In this classical experiment, a clamp placed around one renal artery produced hypertension which disappeared with restitution of the normal arterial flow or surgical removal of the ischemic kidney. A summary of much of the experimental work related to these early studies is presented in a recent symposium (65). Shortly after Goldblatt's work, the clinical implication of this experimentally produced hypertension was reflected by an increasing number of case reports describing nephrectomy in unilateral renal disease complicated by hypertension. Butler in 1937, reported a case of hypertension with unilateral pyelonephritis relieved by nephrectomy (66). In 1938, Leadbetter and Burkland reported an intrarenal artery mass of smooth muscle causing unilateral renal ischemia and hypertension, which was relieved by nephrectomy (67). Leiter (68) reported thrombarteritis obliterans of one renal artery, Freeman and Hartley (69) found atheromatous plaques in one renal artery, and Blatt and Page (70) noted tumor compressing one renal artery, all having produced hypertension that was relieved by nephrectomy. During the next decade there was enthusiastic application of these observations and a host of nephrectomies were performed in hypertensive patients with the slightest evidence of a unilateral renal abnormality. Smith, in 1948, collected data from 242 patients but found a beneficial effect in only 19 per cent of cases in which the operation had been performed (57). In 1956, Smith reviewed 575 cases in which unilateral nephrectomy was performed for hypertension (71). The incidence of blood pressure reduction below 140/90 for greater than one year averaged 26 per cent. Smith suggested that the reason for this unimpressive record was the indiscriminate selection of patients. The removal of a single small kidney due to congenital hypoplasia or pyelonephritis, or of a diseased hydro-nephrotic kidney, by no means assures relief of the hypertension. On the other



hand, when the unilateral renal disease is associated with disease of the renal vasculature, the likelihood of cure following nephrectomy appears to be greater. Accordingly, it is essential to devise reliable techniques to detect those patients with unilateral renal arterial disease.

Renal artery obstruction may be caused by a number of lesions; atheromatous plaque is the most common. Thrombosis, embolus, congenital or acquired stenosis of a renal artery are less common causes. Rarely, extrinsic pressure on the renal vessels by tumor, fibrous bands, or aneurysms narrow the lumen of a renal artery. Microscopic examination of the kidney with the involved artery reveals tubular atrophy, increase in interstitial tissue but only minimal changes of nephrosclerosis. In kidneys removed with subsequent "cure" of the hypertension, Connor *et al.* found "ischemic atrophy"—tubules lined with "altered but living cuboidal cells" (72). This was contrasted to dilated "thyroid-like" tubules lined with "flattened and inactive cells" seen in pyelonephritis. These authors considered the former lesion characteristic of the ischemic kidney. It is generally agreed that hypertension does not follow complete infarction, but rather, the development of ischemic renal tissue and the "ischemic atrophy" described above (52, 73).

The diagnosis of unilateral renal artery disease is frequently difficult to make with certainty. However, a review of the reported cases reveals historical features that appear to be helpful (72, 74, 75). These include:

- 1) the sudden onset of colicky abdominal pain, most often in the flank, which is followed by hypertension;
- 2) the abrupt onset of hypertension in a patient less than thirty or greater than fifty years of age;
- 3) the development of accelerated hypertension in a patient greater than sixty years of age;
- 4) the change of a pre-existing mild hypertension to a rapidly progressive severe form.

Physical findings are similar to those in patients with hypertension of comparable severity and duration from any cause. Rarely, a bruit may be heard in the abdomen, most often in the costolumbar area.

The most promising techniques for the recognition of unilateral renal artery disease include:

- 1) bilateral ureteral catheterization;
- 2) radiographic test, specifically, intravenous pyelography, "timed" intravenous pyelography, retrograde pyelography, and renal angiography;
- 3) nephrogram with radioactive-tagged substances;
- 4) use of diagnostic antihypertensive drugs.

### 1. Bilateral Ureteral Catheterization

Mueller *et al.* reported that constriction of the lumen of one renal artery in the dog caused a decrease of urine volume and sodium concentration of the urine from that kidney as compared with the contralateral unaffected kidney (76). Based on these studies, Howard and his collaborators devised a renal function

test for detecting unilateral renal disease (72, 77). In this test, the urine is collected simultaneously from separate ureteral catheters, and the rate of urine formation and concentration of sodium in the urine from each kidney are compared. Four groups of patients were studied by these authors. In the first group which consisted of patients with essential hypertension with no history or evidence of renal disease, the urine obtained from both kidneys was virtually identical in volume and salt concentration. In the second group which consisted of hypertensive patients with bilateral intrinsic renal disease, the urine volumes were occasionally unequal, but the sodium concentration was either the same or slightly greater on the side of the smaller volume. The third group consisted primarily of patients with unilateral renal disease in whom nephrectomy had relieved the hypertension. The urine obtained from the diseased kidney was reduced in volume and sodium concentration as compared to the contralateral kidney. The fourth group of patients were those with unilateral intrinsic renal disease, generally of the pyelonephritic type, and hypertension in whom nephrectomy did not affect the hypertension. In these cases, the diseased kidney produced a urine of smaller volume, but with a sodium concentration equal or greater than that of urine from the contralateral kidney. The authors concluded that in a case of unilateral renal disease with hypertension, smaller volume and lower sodium concentration in the urine from the diseased kidney represented a "positive test" and suggested that nephrectomy would improve the hypertension. A differential greater than fifty per cent in urine flow and greater than fifteen per cent in sodium concentration between the two sides was considered significant.

Page, Dustan and Poutasse reported the results of a bilateral catheterization procedure in three clinical groups: essential hypertension, pyelonephritis, and renal artery disease (75). In ten patients with essential hypertension the urine flow, glomerular filtration rate, urine sodium concentration and urine osmolality were similar bilaterally. In patients with pyelonephritis, urine flow and urine osmolality were lower on the most affected side; sodium concentration was essentially the same bilaterally. In cases of unilateral renal artery disease, the affected kidney produced a smaller volume of urine with increased osmolality. Urine sodium concentration on the affected side ranged between 20 to 40 per cent less than on the contralateral side. In cases with bilateral renal artery disease, comparison of the rate of urine flow and urinary sodium concentration from the two kidneys gave variable results. In some patients, urine sodium concentration was higher on the side of low urine flow; in others, urine sodium concentration was lower on the side of low urine flow and in one case urine sodium concentration was the same on both sides. In cases with disease in the major branches of the renal artery with renal infarction, the results were similar to those obtained with pyelonephritis. From this study, the authors concluded that since bilateral and unilateral renal artery disease could give similar results and disease of a major branch of a renal artery could not be differentiated from pyelonephritis, bilateral ureteral catheterization was a poor test for diagnosing unilateral renal artery disease. Baldwin, Hulet *et al.* studied

kidney function by bilateral catheterization in patients free of renal disease and in patients with essential hypertension (78). In a minority of the normotensive patients there were small differences in sodium excretion and urine osmolality. A greater disparity between the two kidneys was found in the patients with essential hypertension; this was noted early in the disease. These authors concluded that the hypertension may affect the two kidneys unequally. This functional difference demonstrated in essential hypertension cast doubt on the validity of bilateral ureteral catheterization as a technique for diagnosing unilateral renal artery disease. Despite these contradictory findings, it is now generally accepted that when the bilateral ureteral catheterization test is performed as recommended by the original workers (72), a marked reduction in urine volume and sodium concentration observed on the involved side, suggests that nephrectomy or correction of the circulatory defect will improve the hypertension.

## *2. Radiographic Techniques*

### *A. Intravenous Pyelography*

Intravenous pyelography is a useful screening test in the diagnostic workup for unilateral renal artery disease. If the routine abdominal x-ray reveals one kidney shadow to be smaller than the other, and if there is poor or no visualization of dye on that side, this is presumptive evidence of unilateral renal disease. Similarly, delayed visualization of the dye on one side suggests unilateral renal disease (79). Recently, however, a number of reports have emphasized that equal bilateral visualization may occur despite the presence of unilateral renal disease (75, 80).

### *B. Retrograde Pyelography*

This procedure may be of value when intravenous pyelography has revealed nonvisualization or delayed excretion of dye on one side. Under these conditions, a normal retrograde pyelogram suggests that there is obstruction of one renal artery. Furthermore, with this technique, the clubbed calyces, characteristic of pyelonephritis, or the calyceal atrophy, occasionally seen with occlusive disease of the renal artery, may be observed.

### *C. Renal Angiography*

Visualization of the renal vessels with radiopaque media is the most dependable procedure for demonstrating abnormalities of these vessels. The method most frequently employed is intra-aortic injection of the dye via a translumbar route (81). Numerous other approaches have been described (82). Dustan and Poutasse studied 104 cases of hypertension with renal angiography, and demonstrated occlusive disease of the renal arteries in thirty patients (83). In 23 of these 30 cases the obstruction was due to an atherosclerotic plaque. The disease was unilateral in 17 cases. In six studies poststenotic dilatation was present.

Indications for aortography have been outlined by Page, Dustan and Poutasse (75). These include: disparity in size or excretory function of the two kidneys, as shown in the intravenous pyelogram, hypertension in young patients without a family history of hypertension, middle-aged or elderly hypertensive patients whose disease enters a malignant phase, malignant hypertension occurring in a patient without a history of mild essential hypertension and hypertensive disease in a patient of any age whose hypertension suddenly becomes severe.

Unfortunately, aortography is not without risk. Injection of a large amount of contrast media directly into a renal artery may lead to renal damage. McAfee in a review of complications of abdominal aortography reported twelve fatal cases due to renal failure (84). Neurologic complications, which are not uncommon, have been reported, and include paraplegia, foot drop and transverse myelitis (85). Gastrointestinal complications, including infarction of the bowel and acute pancreatitis, have resulted from injection of dye directly into the celiac or mesenteric vessels. Other less common complications are severe hemorrhage at the aortic puncture site, shock, dissecting aneurysm of the aorta and retroperitoneal infection (84). Methods to insure greater safety have led to several technical modifications. A preliminary film after the injection of a small amount of dye will reveal the correct positioning of the needle. Poutasse, in order to decrease the quantity of dye that need be injected, reduced the blood pressure acutely with antihypertensive agents (86). Steinberg *et al.* introduced a method for the rapid intravenous administration of a large quantity of contrast media for visualization of the abdominal aorta and renal vessels (87).

### 3. *Nephrogram with Radioactive-tagged Substances*

Winter, in 1957, utilized radioactive diodrast to obtain a radioactive renogram in 44 hypertensive patients (88). In ten patients in whom unilateral abnormalities were found, bilateral ureteral catheterization, aortography or intravenous pyelography were done. The excellent correlation between these tests and the radioactive renogram led the author to conclude that this technique provided a good screening test for detecting unilateral renal disease. The safety and reliability of this procedure as a preliminary screening test has been emphasized by other workers (89).

### 4. *Use of Diagnostic Antihypertensive Drugs*

Brust and Ferris reported the use of a ganglionic blocking agent (tetraethylammonium chloride-TEAC) to differentiate hypertension associated with renal parenchymal disease from that seen with primary unilateral renal vascular disease (90). In the former group, the administration of TEAC produced a fall in blood pressure, while in the latter group the drug caused no change or a rise in blood pressure. In this study, nephrectomy was performed in ten patients with unilateral renal disease, in five of whom the TEAC test had suggested the presence of a "vascular lesion" and in five a "parenchymal lesion". In four of



the five patients with the "vascular lesion", nephrectomy resulted in a "cure" of the hypertension, while in all five of the patients with a "parenchymal lesion" nephrectomy caused no change in blood pressure. The authors suggested that this test might be useful preoperatively to determine if a demonstrable unilateral renal lesion was responsible for the hypertension and to predict whether nephrectomy would relieve the hypertensive process. The small number of cases prevents complete acceptance of these conclusions, but the results are of interest and further studies are warranted.

From the many available techniques and the conflicting reports concerning the reliability and prognostic implications of each diagnostic method, it may be difficult for the attending physician to choose a proper course of action. It seems appropriate that in any patient under the age of forty years with sustained and markedly elevated hypertension, particularly if of recent onset, unilateral renal artery disease should be excluded. On the basis of widening experience, it is becoming evident that the most reliable procedure is that of aortography. Under conditions where this procedure has been performed repeatedly with the virtual elimination of major complications, it is emerging as the definitive technique. When indications are less precise, bilateral ureteral catheterization may offer a reliable method if performed as originally recommended and if interpreted as "positive" only when the difference between the two sides is distinct. Alternatively, in those patients where the hypertension is of much milder degree, more gradual in development and responsive to adequate medical management, the physician may depend upon intravenous pyelography or radioactive nephrogram, to help exclude the possibility of unilateral renal artery disease. However, he must be ready to resort to the more definitive tests if acceleration of the disease occurs despite adequate supervision. Finally, in those patients who have obvious intrinsic unilateral renal disease in association with accelerated hypertension, but in whom the aortogram or bilateral ureteral catheterizations do not support the diagnosis of large vessel occlusive disease, nephrectomy may have to be performed as a final resort.

#### RADIATION NEPHRITIS

A variety of clinical syndromes have been observed following irradiation to the area of the kidneys in dosage greater than 2000 r (91, 92). The picture may range from a relatively acute illness, characterized by severe hypertension and its sequelae with superimposed uremia producing fatality in one-half of the subjects to only a modest hypertension associated with meager proteinuria and relatively well preserved renal function. In some cases, the disease may be protracted and indistinguishable from chronic glomerulonephritis. Rarely, a clinical syndrome like that of a malignant phase of hypertension may be noted. The mechanism for the production of the hypertension in radiation nephritis has been related to the experimental work by Page (93) in which perirenal cellophane wrapping caused a perinephritis, renal ischemia and hypertension (91). In fact, three case reports have appeared in which severe hypertension was associated with unilateral radiation nephritis and was relieved



by nephrectomy (94-96). It is of importance to remember this syndrome as a cause of severe hypertension despite its relative infrequency.

#### RENAL AMYLOIDOSIS

Classically, amyloid disease of the kidney is associated with a nephrotic syndrome, with low or normal blood pressures, despite the development of progressive renal failure. In a review of the literature up to 1950, only 39 cases of hypertension associated with renal amyloidosis could be found (97). In a more recent series, 8 out of 39 cases of renal amyloidosis were complicated by hypertension (98). While the majority of cases die with apparently normal blood pressures, it must be remembered that amyloidosis is often a complication of a debilitating disease (i.e. tuberculosis, osteomyelitis, rheumatoid arthritis) and in such illnesses the blood pressure tends to be low. Nevertheless, renal amyloidosis rarely produces modest constriction of both kidneys, which is associated with a clinical picture of malignant hypertension superimposed on the other features of renal amyloidosis (99).

#### *Systemic Diseases with Renal Involvement*

A number of systemic diseases of unknown etiology affect the renal vasculature diffusely and may be associated with hypertension. A brief description of the characteristics of this form of hypertension is presented.

#### POLYARTERITIS NODOSA

Hypertension is a common feature of the renal involvement seen in polyarteritis nodosa. The renal manifestations of the disease may initially present with a clinical picture that includes proteinuria, hematuria and renal insufficiency. The blood pressure at this time may be normal. However, progressive renal failure and hypertension soon follow and the picture may then be indistinguishable from chronic glomerulonephritis. Another form mimics the malignant phase of hypertension, with hypertensive retinopathy, marked renal failure and irreversible uremia.

Attempts to correlate the hypertension with anatomic changes in the kidney have led investigators to varying conclusions. Davson, Ball and Platt concluded that the renal findings bore no relation to the presence of hypertension (100), while Rose and Spencer found that the presence of healed fibrotic vascular lesions were more common in subjects with hypertension, and suggested that the "healed lesion" led to "ischemic fibrosis" and hypertension (101).

The diagnosis of polyarteritis nodosa should be considered in any case with severe hypertension and progressive renal failure associated with evidence of a constitutional illness (fever, weight loss, leukocytosis and elevated erythrocyte sedimentation rate).

#### SYSTEMIC LUPUS ERYTHEMATOSUS

The association of systemic lupus erythematosus and hypertension appears to be uncommon (102-104). While hypertension may occur during the develop-

ment of severe renal insufficiency, marked renal failure frequently occurs without hypertension.

#### SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Only recently has it become evident that renal involvement occurs in scleroderma (105). Characteristic sclerotic, fibrous lesions, affecting chiefly the interlobular arteries and the arterioles, have been described (105-107). The clinical course of the renal involvement may be protracted and benign, but more commonly it is acute and fulminating (108). The degree of the hypertension generally relates to the severity of the renal failure, but occasionally the hypertension precedes overt evidence of renal involvement. Once the renal disease becomes manifest, malignant hypertension with death in uremia may supervene.

#### DIABETIC GLOMERULOSCLEROSIS

In 1936, Kimmelstiel and Wilson reported a series of cases to illustrate a relation between diabetes mellitus complicated by edema, proteinuria and hypertension, and a type of nodular sclerosis of the glomeruli called intercapillary glomerulosclerosis (109). Much controversy has arisen as to the specificity of the histologic lesion and the definition of this syndrome as a clinical entity (110-114).

The incidence of hypertension in patients who at postmortem examination show characteristic lesions of intercapillary glomerulosclerosis ranges between 50 to 65 per cent of cases (115, 116). Several groups of investigators have found hypertension twice as common in diabetic patients with intercapillary glomerulonephritis than those without this lesion (114-117). Despite this greater incidence in the presence of intercapillary glomerulosclerosis, the hypertension can best be correlated with the severity of the atherosclerotic vascular lesions and not the glomerular lesions (111, 118).

#### SUMMARY

The clinical characteristics of the hypertension associated with intrinsic diseases of the kidney are reviewed in detail and a brief summary of the characteristics of the hypertension seen in those systemic diseases affecting the renal vasculature secondarily is presented. Diagnostic techniques, particularly those useful in unilateral renal disease, are described. A program for the management of the hypertension associated with intrinsic renal disease is outlined. The potential dangers from the use of antihypertensive agents in the presence of marked renal insufficiency are emphasized. The syndrome in which intrinsic renal disease presents primarily with the manifestations of hypertension in the face of well preserved renal function, is described in detail.

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## THE DIAGNOSIS OF PHEOCHROMOCYTOMA

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Pheochromocytoma, an almost uniformly fatal tumor (1-3) prior to its first successful resection in 1927 (4), has attained greater importance than its relative rarity would appear to warrant, because of the comparative ease with which the hypertension associated with it can be cured or ameliorated in the majority of instances. A rare condition, the recognition of which can be lifesaving, demands uniformly accurate and reliable diagnostic techniques. Until 1945 (5) however, the recognition of this disease depended upon clinical acumen alone, and even today, the manifold and capricious signs and symptoms of this catecholamine producing tumor must first impress the physician enough to warrant a somewhat cumbersome investigation (6-11) to prove its presence.

Recent advances in knowledge of catecholamine metabolism have greatly simplified the diagnosis of pheochromocytoma (12-14). This necessitates a critical evaluation of the means by which this diagnosis is first suspected and finally established.

### VARIABILITY OF CLINICAL SYNDROMES WITH PHEOCHROMOCYTOMA

Over 98 per cent of pheochromocytomas are intra-abdominal (15), the remainder most frequently arising in the chest. Only two reported extra-abdominal pheochromocytomas, one cervical and one intracranial, failed to be visualized by roentgenographic examination of the chest (16, 17). About ninety per cent of the tumors occur in or about the adrenal glands (1, 6, 10, 11, 16, 18-22), the right being affected twice as frequently as the left (15, 23). Multiple pheochromocytomas occur in 6 to 48 per cent (average, twenty per cent) of the patients, the higher figure occurring in the younger age group (10, 11, 15, 16, 19, 22, 24). The tumors vary in size from 0.5 to 28 cm in diameter, and in weight from 1 to 3167 Gm (1, 3, 10, 11, 19, 21). It must be emphasized that the majority of pheochromocytomas are small, weighing under 100 Gm (7, 21). No relationship of tumor size to function has been demonstrated (3). Extra-adrenal abdominal tumors may be present near the paraganglia (15, 18), the aortic bifurcation (organ of Zuckerkandl) (6, 11, 20), the urinary bladder (6, 25, 26), or even adjacent to the liver (6). No more than 10 to 15 per cent of these tumors are palpable, although an equal number may yield a paroxysm when massaged (1, 7, 11, 15, 20, 24, 27). It is of interest that only  $\frac{1}{2}$  of the palpable tumors will give rise to a paroxysm when massaged and that only  $\frac{1}{2}$  of those tumors yielding such a paroxysm are palpable (15). The description of the

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Aided by grants from the American Heart Association and the National Heart Institute (H-1164, H-A-4477).



pathology of pheochromocytoma should serve to emphasize the improbability of adequate delineation of the lesion by physical examination alone.

Thus the physician has been enjoined to suspect pheochromocytoma in the presence of a suggestive history or certain nondiagnostic physical and laboratory findings, namely:

### 1) *Hypertension*

- a) present in from 80 (3) to 90 (25) per cent of cases (28-34);
- b) paroxysmal in from 22 (7) to 87 (15) per cent of cases (1, 3, 8, 11, 35-39);
- c) often complicated by symptoms of a severe or sudden rise in blood pressure, such as headache (11, 19, 39, 40) (55 per cent) (15), palpitation (11, 40) (38 per cent) (15), dyspnea (19 (15) to 27 (39) per cent), visual disturbance (10, 19, 41, 42) (8 (15) per cent), coma (10) or convulsion (43);
- d) sometimes associated with a paradoxical rise in blood pressure following a therapeutic trial with ganglioplegic drugs (35, 44);
- e) at times severely aggravated by minimal trauma (41), childbirth (41) (50 (45) per cent mortality), preanesthetic or anesthetic medication (41, 44, 46-48), or surgery (35, 41, 49, 50);
- f) sometimes associated with postural hypotension or tachycardia (11, 15) (44-50 (8) per cent);
- g) frequently complicated by cardiac (10, 15, 36) (50 (39) per cent), retinal (11, 15) (80 (15)-100 (39) per cent), and cerebrovascular abnormalities (11) (14 (51) to 26 (15) per cent); less frequently complicated by renal vascular damage (52) (9 (39) per cent);

### 2) *Hypermetabolic State*

- a) weight loss (19) or inability to gain weight (35) (33 (39) per cent), less frequent in children (53);
- b) excessive perspiration (8, 19, 39) (23 (15) to 78 (40) per cent);
- c) BMR increased above +20 per cent (1, 8, 35, 37, 54) (50 (15) per cent);
- d) glycosuria (1) (18 (24) per cent); hyperglycemia (1, 8, 35, 37, 55) (40 (15) to 78 (54) per cent); abnormal glucose tolerance (25 to 40 per cent) (37, 55);
- e) fever (10, 27) (18 (39) to 78 (8) per cent);
- f) tremulousness (10);

### 3) *Paroxysms*

- a) peripheral vasomotor phenomena, such as paresthesias, pallor or blanching, flushing, and sensations of coldness in extremities or face (11, 19) (47-94 (8, 40) per cent);
- b) thoracic pain (11) (12 (15) to 27 (39) per cent);
- c) abdominal pain (11, 19, 20, 39, 56, 57, 58) (15 (20) per cent);
- d) pain in extremities (11, 39);

- e) nausea (90 (40) per cent), vomiting (15, 58) (33 (39) per cent), or gastrointestinal hemorrhage (19, 33, 59);
- f) sensation of great anxiety (11, 19, 60) (50 (39) per cent);
- g) hematuria (in 6 of 9 cases with tumors within the urinary tract) (25);

#### 4) *Neurocutaneous Syndromes*

- a) pheochromocytoma present in 10 per cent of patients with von Recklinghausen's neurofibromatosis (11, 22, 56, 61);
  - b) rarely associated with von Hippel-Lindau disease (61);
- 5) Miscellaneous symptoms such as weakness (15, 19, 39), polyuria and polydipsia (especially in children) (15, 19, 62), urinary frequency and nocturia (10);
- 6) Miscellaneous physical findings, such as goiter (1, 15, 39, 40) and mydriasis (10).

The significant frequency of normotension with these tumors is attested to by the numerous descriptions of pheochromocytomas whose recognition by chest x-ray (32) or gastrointestinal symptomatology (33) precedes any rise in blood pressure. Moreover, when pheochromocytomas are malignant (11 (15) per cent) or when they are first suspected at autopsy, normal blood pressure may have been present in from 11.8 (28) to 40 (30, 34) per cent of the cases. A pheochromocytoma may even be rich in catecholamines without hypertension being observed prior to resection (32).

In the light of a clinical picture of such variability, it is not surprising that Smithwick, in 1950, should hold that pheochromocytoma "... has been principally an autopsy diagnosis". There is small cause for satisfaction in the 76 to 78 per cent of pheochromocytomas detected at autopsy (22, 63) prior to the era of pharmacologic tests (1945), and the 60 to 70 per cent similarly discovered and described after 1950 (8, 47, 64). Large series of patients have been described whose tumors went undetected until postmortem examination (3, 29), despite the presence of hypertension and other suggestive clinical findings. In fact, 0.45 per cent of those patients undergoing a routine lumbodorsal splanchnicectomy for hypertension were found to be harboring a previously unsuspected pheochromocytoma (15). The incidence of pheochromocytoma is no more than 0.5 (65) to 0.6 (66) per cent in those patients specially referred for pharmacological and chemical tests to detect this tumor. When corrected for the estimated incidence of hypertension in the general population (40, 67, 68), the 0.1 (3)–0.25 (29) per cent frequency of these tumors in serial routine autopsies suggests that the clinical acumen is so poor as to permit us to refer no more patients with pheochromocytomas for special testing, than we are leaving behind in the untested hypertensive population.

Equally disturbing though less frequently seen, are those patients with clinical findings strongly suggestive of pheochromocytoma, but who fail to reveal a tumor when surgically explored (69). Even in the hands of those most experienced in the detection of these tumors, the frequency of such negative explorations has been as high as 20 (6) to 25 (70) per cent.

Not only has this tumor been diagnosed when it was not present and ignored

when it was present, but it has also earned the label "great mimic" (6, 41, 71, 72) by being mistaken for: primary (essential) hypertension (3, 8, 11, 15, 27, 35, 37, 44, 73), renal hypertension (25, 39, 52, 73), thyrotoxicosis (10, 66), an anxiety state (10, 16, 44, 60), a menopausal syndrome (40), a fever of unknown etiology (39), diabetes (31, 39, 74, 75), an insulinoma (hypoglycemia) (15, 40), epilepsy (15, 31), a brain tumor (10, 31, 44), migraine (66), angina pectoris with or without aortic valvular insufficiency (10, 40, 66), a renal neoplasm (31), plumbism (10, 15), tabes dorsalis (15, 31), a cerebrovascular accident (31), aortitis (31), an allergy (15), a Waterhouse-Friderichsen syndrome (37), mediastinal lymphoma (40), meningitis (10), polyarteritis nodosa (10), duodenal ulcer (59, 76), toxemia of pregnancy (45, 77), Kimmelstiel-Wilson syndrome (21, 78), biliary tract disease (76), Cushing's syndrome (39, 71), gastrointestinal hemorrhage (59, 79), perforation of small bowel with peritonitis (59, 79), rheumatic heart disease (39), and undoubtedly other conditions.

The need for an inexpensive, harmless, but accurate test which could be readily utilized to detect the presence of a pheochromocytoma in a patient with *minimal* suggestive symptomatology has been obvious. The first successful attempt in this direction was the discovery of the histamine test in 1945 (5).

## II. PHARMACOLOGIC TESTS

The use of a drug to detect the presence of a pheochromocytoma by eliciting a paroxysmal increase in blood pressure was initially described by Roth and Kvale in 1945 (5). In 1948, mecholyl (acetyl- $\beta$ -methylcholine) (80) and tetraethylammonium bromide (81) were suggested in place of histamine for so-called provocative testing. In view of the frequency of sustained hypertension in association with pheochromocytoma, pharmacologic testing made a significant advance in 1947 with the description by Goldenberg, Snyder and Aranow of an agent, piperoxan, which could detect this tumor by eliciting a specific fall in the subject's blood pressure (82). Phentolamine (83, 84) and dibenamine (85) were also felt to be capable of eliciting a fall in an elevated blood pressure in the presence of a pheochromocytoma, but not when the subject suffered from other conditions associated with hypertension.

These tests, the methods for their performance, their reliability, and their toxicity demand detailed examination. In the performance of any of the following, it is good practice to start an intravenous drip one half hour prior to administration of the drug, during which time careful baseline blood pressures of both upper extremities are obtained (6). The test drug and any antidote may be administered via the intravenous needle already in place.

### A. Histamine

1) *Indication*: This is a provocative test (5) to be used when the subject's blood pressure does not exceed 150-170/110 (6, 9, 27, 44, 65, 66).

2) *Method*: From 0.025 to 0.050 mg of histamine base is rapidly administered intravenously. If the presence of a pheochromocytoma is strongly suspected, as low as 0.010 mg of histamine base may be given initially (86). Prior to this

test, a routine cold pressor test must be performed by placing the subject's hand and forearm into water at 4°C for one minute, following which the blood pressure is observed at ½ minute intervals for five minutes (6, 9, 11, 15, 65, 87). Following administration of histamine, the blood pressure must be observed every half minute for five minutes and every minute for ten minutes longer (6, 11).

3) *Response Indicative of a Pheochromocytoma*: A blood pressure rise greater than 60/30–40 occurring within one-half to two minutes, or at most four minutes, which pressor response exceeds that of the cold pressor test, is considered a positive test (6, 9, 10, 11).

4) *False Positive and Negative Responses*: Individual series have revealed false negative test results in 13 (38) per cent, 14 (15) per cent, 20 (49) per cent, 22 (9) per cent, 25 (88) per cent, and 29 (1) per cent of patients proved to harbor a pheochromocytoma. Although a slow rate of histamine injection has been held responsible for occasional false negative results (27), there is little doubt but that such results may be observed when the test is carried out properly and even repeatedly (18, 27).

False positive responses to histamine have been estimated to occur in 2 to 7 per cent of clinically suspect subjects failing to have a pheochrome tumor (70, 89). Chapman and Singh (9) felt that false positive results were quite rare, only two such instances having been described prior to 1954, but Aranow, in 1952, considered these results to be "frequent" (11). Since 1955, Henry and Sobel (90), Roth *et al.* (60), and Orgain (27) have all described false positive histamine tests, these being most apt to occur after administration of sedatives. Although some have held this test to be unreliable (42), it is generally accepted today as the most specific of the provocative tests for the detection of a pheochromocytoma (16, 44, 91).

5) *Side Effects*: Not only is severe headache or other discomfort a frequent complication of this test in subjects with essential hypertension, but the induction of a paroxysm in the patient with a pheochromocytoma can be life threatening (9, 16). At least two deaths have followed the administration of histamine in this manner (38), and some consider the test too dangerous for routine clinical use (40). To counteract the occasional but violent reaction to histamine, 5 mg or more, of phentolamine may be promptly administered intravenously (44, 92). Certainly the side effects of this test have restricted its widespread acceptance as a routine screening procedure to be applied to all patients with a history of paroxysmal symptoms. Moreover, it is probable that about half the patients with pheochrome tumors are not appropriate subjects for this test because of sustained hypertension.

### *B. Tetraethyl ammonium chloride or bromide (TEAC)*

1) *Indication*: This provocative test, originally described by LaDue, Muriison, and Pack in 1948 (81), can be used when the subject's blood pressure does not exceed 150–170/110.

2) *Method*: Following performance of a cold pressor test, 400 mg of TEAC



is administered intravenously (11). The blood pressure is determined every half minute for five minutes and every minute thereafter until at least fifteen minutes after the injection.

3) *Response Indicative of a Pheochromocytoma*: A rise in blood pressure exceeding that following the cold pressor test (11) and persisting for about fifteen minutes can be considered a positive test.

4) *False Positive and Negative Responses*: False negative tests have occurred in as many as seventy per cent of subjects harboring pheochromocytomas (9). Evans' series of 218 tests revealed nine false positive results (93). The high incidence of false negative results makes it even unsuitable for use as a screening test for those subjects without severe hypertension. Its general unreliability has resulted in its infrequent use (10, 11, 27, 42, 86).

5) *Side Effects*: In their original description (81), LaDue, Murison and Paek stressed the advantage of tetraethylammonium bromide over histamine in that the untoward results of a paroxysmal rise in blood pressure could be counteracted by eliciting the postural hypotensive effect of the former drug, that is, by having the patient sit or stand. Unfortunately, severe toxic side effects (11, 94) and even death (27, 95) were soon found to be occasional sequelae of the administration of this substance. Cardiac arrhythmias and severe hypotensive reactions have been observed repeatedly (11, 27, 94, 96).

#### *C. Acetyl- $\beta$ methylcholine (methacholine or mecholyl)*

1) *Indication*: This provocative test, originally described by Guarneri and Evans in 1948 (80), is for use in subjects whose blood pressure is below 150/110.

2) *Method*: The subcutaneous administration of 25 mg of mecholyl (80) elicited toxicity severe enough to warrant reduction of the test dose to 10 mg (10, 11) and either premedication with or inclusion of 1 mg of atropine to reduce muscarinic side effects (10, 16, 80). Blood pressures must be determined at one minute intervals for thirty minutes after administration of the drug (11).

3) *Response Indicative of a Pheochromocytoma*: A slight fall in blood pressure followed rapidly by "a marked and more sustained rise to hypertensive levels constitutes a positive test" (80). Aranow considered positive only those pressor responses exceeding the results of cold pressor tests (11).

4) *False Positive and Negative Results*: Guaneri and Evans performed the test upon 27 control subjects without observing a false positive result (80). Chapman and Singh, however, found that four of six of their patients with pheochromocytomas had false negative results with this test (9). Its general unreliability has been noted frequently (9-11, 86, 88, 97). The absence of more significant data is probably a consequence of the infrequent use of this compound because of its toxicity.

5) *Side Effects*: Angina pectoris, convulsive seizures, hypotensive episodes, electrocardiographic changes, and death have been reported following administration of this substance (10, 21, 80, 86, 97, 98). Serious toxicity and lack of reliability have almost completely disposed of this test.

*D. Phentolamine (2-(N-p-tolyl-N-(m-hydroxyphenyl)-aminomethyl)—imidazoline hydrochloride)*

1) *Indication:* Since the majority of patients with pheochromocytomas have sustained hypertension, a screening test based upon reduction of the blood pressure should have broad applicability. Iseri (84) and Emlet (83) and their respective co-workers, in 1951, advocated the use of phentolamine as such a test for screening hypertensive subjects (blood pressure more than 170/100 (66)) for the detection of pheochromic tumors.

2) *Method:* Five mg of phentolamine are rapidly injected intravenously (9), following which the blood pressure is measured every half minute for ten minutes thereafter. The results after intramuscular administration of phentolamine have been found to be too unreliable for it to serve as a diagnostic test (9, 86).

3) *Response Indicative of a Pheochromocytoma:* A fall in blood pressure of 35/25 or greater within two minutes following the injection is considered a positive test (9).

4) *False Positive and Negative Responses:* False positive test results have been described in 7 (27) per cent, 10–17 (70) per cent, 10 (38) per cent, 10–20 (89) per cent, 25 (99) per cent, 30 (100) per cent, and 43 (90) per cent of hypertensive subjects without pheochromocytomas. The incidence of false positive results has been shown to increase markedly in the presence of azotemia or premedication with narcotics, sedatives or vasoconstrictor agents. Even mild azotemia may interfere with this test. Overdosage must be avoided since phentolamine, in large enough quantities, is also capable of lowering blood pressure in essential hypertension (9, 27). Although held to be less frequent than false positive results (27, 49, 86, 101), false negative phentolamine tests have been observed in 17 (38) to 20 (9) per cent of patients with proved pheochromocytomas. Such results may be especially frequent following antihypertensive therapy (6, 66). It has been estimated that discontinuance of narcotic, sedative, vasoconstrictor and antihypertensive agents for from two to fourteen days prior to the phentolamine test should afford greatest reliability (6, 27, 66, 91), but misleading results can nonetheless occur (20, 27, 86).

5) *Side Effects:* Although phentolamine has been considered to be the safest agent for the routine screening of hypertensive subjects for detection of pheochromocytomas (27, 91), serious toxicity (21, 70) and occasional fatalities have been reported (45, 101, 102). Mild tachycardia has been frequently observed and an increase in blood pressure or irreversible shock has occasionally been seen (21). Shock has resulted from as little as one mg of phentolamine administered intravenously to a patient with a pheochromocytoma (103). The presence of angina pectoris, cardiac arrhythmia, or "threatened" cerebrovascular accident represents a contraindication to the performance of a phentolamine test (70). Nevertheless, this test compares favorably with other such procedures in both safety and reliability, and has become the one most frequently used for routine screening of hypertensive subjects (27, 91).

*E. Piperoxan (piperidyl methyl benzodioxane)*

1) *Indication:* Piperoxan, the first agent recommended for the detection of a chromaffin tumor in a subject with sustained hypertension (82), may be administered to any patient whose blood pressure exceeds 170/110 (27).

2) *Method:* Either 10 mg of piperoxan per square meter of body surface (11) or 0.25 mg per kg of body weight (9, 10), neither to exceed a total of 20 mg, are administered intravenously over a two minute period. The patient's blood pressure must be observed every half minute for five minutes, and every minute for ten minutes thereafter.

3) *Response Indicative of a Pheochromocytoma:* A fall in blood pressure of more than 30/20 (10), 35/25 (27), or 30/30 (9) one to four minutes after the injection constitutes a positive test. The original workers favor graphic representation of this test by plotting blood pressure versus time. When the area beneath the extension of the control blood pressure into the postinjection period exceeds that above this level, the result is considered positive (11). Other workers maintain that an antidiuretic response to administration of piperoxan suggests the presence of a pheochromocytoma (104).

4) *False Positive and Negative Responses:* Although the incidence of false positive results from piperoxan testing is believed to be less than three per cent (38, 89), the presence of azotemia may increase this figure to forty per cent (9). Premedication with sedatives or narcotics as well as the presence of renoprival hypertension can be associated with false positive test results (10, 27, 53). Negative results in the presence of a pheochromocytoma occur with much greater frequency (10, 38, 54, 83, 105), the estimates ranging from 5 per cent (89) to 32 per cent (9). Thus, the frequency of false negative tests with piperoxan far exceeds that with phentolamine.

5) *Side Effects:* About 25 per cent of patients with essential hypertension who undergo pharmacologic testing with piperoxan experience untoward pressor reactions with appreciable discomfort (9, 11). Pulmonary edema, hypertensive encephalopathy, and generalized convulsions can occur frequently enough to make this agent unsuitable for routine screening of hypertensive patients (27, 44, 69, 94, 106).

*F. Dibenamine (N,N-dibenzyl- $\beta$ -chlorethylamine) and dibenzyline*

1) *Indication:* Spear and Griswold, in 1948, suggested that dibenamine be used to test patients with sustained hypertension for the presence of a pheochromocytoma (85). No large series of patients have been studied in this manner, and specific indications as well as criteria for evaluating test results are not available.

2) *Method:* One mg of dibenzyline per kg of body weight is dissolved in 500 ml of 5 per cent glucose in saline solution and administered intravenously for a period of approximately one hour (85, 107, 108).

3) *Response Indicative of a Pheochromocytoma:* No reliable criteria of a positive test are available, but an appreciable fall in blood pressure should be observed (85). Some workers feel that a positive histamine test which becomes

negative after a dibenzyline infusion strongly favors a diagnosis of pheochromocytoma (85, 107, 108).

4) *False Positive and Negative Responses:* Published studies do not offer data adequate for statistical evaluation, but the consensus is that dibenamine and dibenzyline are capable of lowering the blood pressure in patients with essential hypertension as well as in those with pheochromocytomas (9, 88). The test appears to be unreliable (9, 11, 27).

5) *Side Effects:* Orgain (27) and Bierman and Partridge (94) maintain that this test is potentially dangerous. These drugs can cause severe and persistent hypotension (94), as well as excessive central nervous system stimulation (107).

#### *G. Other substances suggested for use in the detection of chromaffin tumors*

Amytal (21), epinephrine (15), 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) (109), and ganglioplegic drugs (35, 44) have all provoked hypertensive paroxysms in the presence of a pheochromocytoma. The demonstration of reduced pressor reactivity to subcutaneous epinephrine in the presence of this tumor (88, 110) suggested that catecholamine hyporeactivity might serve to detect pheochromocytomas.

Very few of these drugs have proved to be reliable enough for continued clinical use in the pharmacologic testing of pheochromocytoma suspects. Roth and Kvale, in summarizing their extensive experience in 1956 (91), favored retaining only two of the pharmacologic agents, histamine and phentolamine, for continued use. In general, these tests have offered no more than 80 to 90 per cent reliability (38, 76), and, in view of their occasional toxicity, they are now gradually being replaced by other diagnostic methods. Marked intolerance to diagnostic and therapeutic manipulations as well as sudden death are found in a disturbingly large number of case histories of patients with pheochromocytomas (11, 19, 39, 40, 46, 49, 90, 100). Wingo (21) observed life threatening paroxysms following no more than a minor change in position of the body of such patients. Any diagnostic procedure which requires a paroxysmal response, whether elicited by palpation or a drug, seems unwise (15, 22). Moreover, any procedure which results in unnecessary manipulation of a patient seriously suspected of having a chromaffin tumor entails a significant and unwarranted risk (17, 37, 44, 49, 111-113).

### III. ROENTGENOLOGIC DETECTION OF PHEOCHROMOCYTOMA

A chromaffin tumor, in that it gives rise to a soft tissue mass in the perirenal area in nine out of ten cases, offers the opportunity for roentgenologic diagnosis and localization by an abdominal flat film, pyelography, tomography, or an air contrast study of the perirenal area. Unfortunately, over 75 per cent of these tumors weigh less than 75 Gm (114) and about one out of every five patients with this disease has more than one tumor (11). Thus, abnormal intravenous pyelograms suggesting a unilateral perirenal tumor may be observed in about twenty per cent (1, 7, 15, 19, 35, 37, 115) (range, 10 (8)-61 (31) per cent) of patients with pheochromocytomas, but it is not at all unusual



for the pyelogram to be suggestive of such a unilateral lesion when either none exists (69, 86) or it is present on the contralateral side or at some distant site (35).

Using the technique described by Carelli in 1921 (116), Cahill (117) favored localization of these tumors by perirenal air insufflation prior to surgical intervention. Rivas, in 1950, introduced a significant technical improvement with the presacral insufflation of oxygen (118). Retroperitoneal pneumography can be expected to localize about fifty per cent (7, 15, 19, 37, 115, 119) of pheochromocytomas but it too, can give rise to seriously misleading results (1, 37, 90). Henry and Sobel reported three out of five patients with essential hypertension who failed to reveal adrenal gland tumors on exploration despite roentgenologic evidence by perirenal insufflation favoring that diagnosis (90). Contrary to pyelography and abdominal flat films, retroperitoneal pneumography carries with it the risk of precipitating a severe and even fatal paroxysm (17, 19, 22, 37, 44, 112). Although insufflation was helpful in localizing pheochromocytomas in 7 of 13 of Clausen's patients, 3 of these 7 suffered "severe reactions" (20). Aortography, similarly used for assistance in localization of these tumors, has also been associated with fatal reactions (111, 113). Since these efforts to localize the intra-abdominal chromaffin tumors at best are but partially successful and, at worst, occasionally misleading (66), it would seem inadvisable to perform such studies routinely upon patients known to tolerate even slight trauma poorly (17, 21, 37, 44, 49). The latest desire to localize pheochromocytomas by intravenous catheterization with differential plasma catecholamine determinations (7, 120, 121) may similarly prove too hazardous for more than very occasional use (17).

The majority of the one to two per cent of extra-abdominal pheochromocytomas are within the thorax, and are visible in the chest x-rays (6, 15, 16, 18, 31, 32, 103). The authors are aware of two instances only in which this tumor was present in the neck, and both patients had had pheochromocytomas removed from the abdomen previously (17, 53, 122). Careful roentgenologic examination of the chest should therefore be a routine procedure for any patient suspected of having a pheochromocytoma.

#### IV. THE DIAGNOSIS OF PHEOCHROMOCYTOMA BY DETERMINATION OF THE CATECHOLAMINES

As long ago as 1937, Beer, King, and Prinzmetal succeeded in demonstrating a circulating pressor substance in a patient with a pheochromocytoma (123). However, the bioassays for epinephrine (E) and norepinephrine (NE) in biologic fluids were relatively crude and nonspecific until shortly before 1950 when Gaddum (124), Burn (125), de Jalon (126), and Goldenberg (54), and their respective co-workers succeeded in developing techniques of sufficient accuracy and sensitivity to permit measurement of plasma and urinary catecholamines. Engel and von Euler, in 1950, first succeeded in demonstrating abnormally high NE excretion in the urine of a patient with pheochromocytoma (127). Their test required sample purification by chemical means and a bioassay for

the final quantitative measurement. Despite continued search for improved biological testing procedures, bioassay for catecholamines has remained a tedious procedure requiring a pharmacologist specifically trained in its performance (70, 128-132).

The best of the bioassay techniques offers a degree of diagnostic reliability approximately equivalent to that of the chemical assays (38, 128). In recent years, a bioassay using a strip of rabbit aorta has had success as a rapid screening test for the presence of pressor substances in urine (70, 129, 133, 134).

Efforts by Lund (135, 136) Weil-Malherbe (137), von Euler (138, 139), Goldenberg (89), Manger (140, 141) and their co-workers to make catecholamine analyses less time consuming and more readily available resulted in the fluorimetric techniques widely used at the present time. These are based upon initial purification of the biologic sample by column chromatography or adsorption of the catechols upon alumina, acid elution and oxidation or conjugation of the catecholamines to form substances more easily quantitated by photofluorimetric means. Obviously they also require highly trained laboratory personnel as well as expensive and intricate equipment. The results of these tests vary considerably because of differences in their specificity (132, 142, 143). Thus, two test procedures may yield markedly different results when analyzing the same biological specimen (132). Moreover, the presence of other fluorescent substances, such as phenothiazine, tetracycline, isoproterenol and perhaps salicylates and other medicinals, can produce falsely high catecholamine analyses with any of the commonly used tests (6, 44, 144). Jaundice, uremia, lymphoblastoma, or even hemolysis of the blood sample may also interfere with certain of these determinations (141). Circumstances which result in high E or NE secretion, such as shock, burns, asphyxia, surgical stress, fever, myocardial infarction, increased intracranial pressure and hypoglycemia, may be expected to result in increased catecholamine excretion (131, 132, 145, 146).

Similarly, administration of antihypertensive and certain tranquilizing drugs, insulin, NE, E, and other medications may modify the quantity of catecholamines excreted (131, 147, 148). Even the collection of the biological sample requires rigorous attention in order that degradation of the catechols be avoided. Acid pH, cold, antioxidants and rapid transport to the laboratory for prompt analysis are required for greatest reliability (131, 132).

No more than a few per cent of E and NE are excreted without significant chemical degradation (115, 131, 149, 150). Even this small quantity may be detected in the urine for no longer than a few hours following a paroxysm (149, 150). Thus, the timing of the specimen collection assumes great importance (6, 44, 114). Plasma catecholamine may be normal within minutes after a paroxysm (114, 141). Normal levels associated with a pheochromocytoma have occurred so often as to necessitate the frequent use of a provocative test (i.e., histamine) in conjunction with the chemical assay (6, 44, 114, 141, 151). Bollman *et al.* (114) observed a patient with a pheochromocytoma who even failed to have an elevated plasma catecholamine level after histamine. Although

Goldenberg claimed that the urine excretion of NE and E remained elevated between the paroxysms of a pheochromocytoma (38), numerous workers have observed normal plasma catecholamines between paroxysms and normal E and NE excretion in the presence of a pheochromocytoma (6, 44, 114, 141, 151). These results are not unexpected in light of the above characteristics of catecholamine metabolism.

Correct interpretation of a catecholamine determination therefore demands that the physician possess a thorough knowledge of the particular chemical procedure used, its normal range of variation and the difficulties likely to be encountered, as well as a general appreciation of human catecholamine metabolism.

The tests in common use today result in normal catecholamine levels under 100  $\mu\text{g}/24$  hour urine collection and 0.1  $\mu\text{g}$  per cent in plasma (89, 152). Pheochromocytoma is usually associated with urine excretions of NE in excess of 300  $\mu\text{g}/24$  hours, but both normal excretion in the presence of a pheochromocytoma (114, 151) and abnormally high excretion in the absence of a pheochromocytoma have been observed (132, 145, 153).

Despite these complexities, the past five years have seen the chemical determination of E and NE in biologic fluids become the single most reliable test for the diagnosis of pheochromocytoma (7). Its cost, inaccuracy when performed by routine clinical laboratories (132) and comparative unavailability have limited its usefulness as a routine screening procedure for detection of these tumors.

#### V. THE DIAGNOSIS OF PHEOCHROMOCYTOMA BY DETERMINATION OF E AND NE METABOLITES

In 1956, Armstrong, Shaw and Wall, while studying the urine phenolic acids by means of paper chromatography, recognized the ability of the human organism to O-methylate the hydroxyl groups of various aromatic compounds (154). In 1957, Armstrong and McMillan identified a product of O-methylation and amine oxidation of NE, 3-methoxy, 4-hydroxymandelic acid (VMA, for vanillylmandelic acid) (12). Shortly thereafter, Axelrod, (155, 156), Sjoerdsma (157), Goodall (149), Resnick (158), Kirshner (150) and their co-workers succeeded in outlining the basic metabolic pathways of E and NE degradation, namely, O-methylation to form metanephrine (M) and normetanephrine (NM), respectively, and amine oxidation of the side chain to form either 3,4-dihydroxymandelic acid (DOMA) or VMA. It now appears that VMA represents the major by-product of E and NE metabolism, with over  $\frac{1}{3}$  of the secreted catecholamine being excreted as VMA (13, 149, 150, 159, 160-162). Studies of isotopically labeled E and NE have demonstrated that whereas E and NE appear in the urine for no more than a few hours after intravenous administration, tagged VMA continues to appear in the urine for at least 24 hours (53, 149, 150). VMA is considerably more stable than E and NE, a fact that simplifies specimen collection (13). Moreover, its excretion is prolonged enough to make 24 hour urine collections unnecessary (13).

The relative stability of VMA, its prolonged period of excretion, and the fact that it exceeds E and NE in the urine by some 10 to 100 fold (13) all suggest the inherent advantage of urinary VMA determination for the diagnosis of pheochromocytoma (159, 163-165).

The most satisfactory semiquantitative test for measurement of VMA is the bidirectional paper chromatographic technique which necessitates no expensive laboratory equipment or specially trained personnel (13, 163, 165). It can be performed on any random urine specimen with a reproducible accuracy of  $\pm 10$  per cent. Normal subjects as well as patients with primary hypertension excrete 1-4  $\mu\text{g}$  VMA/mg creatinine (about 2 to 3 mg per 24 hours). Patients with pheochromocytomas excrete 5 to 40  $\mu\text{g}$  VMA/mg creatinine (mean, 16.5  $\mu\text{g}$  VMA/mg creatinine). Ganglioneuromas and neuroblastomas may also be associated with elevated VMA excretion (166, 167).

Although circumstances which interfere with E and NE formation or metabolism, such as administration of monoamine oxidase inhibitors (168), dehydrogenase inhibitors (169), or certain antihypertensive drugs (147), or the presence of shock, pulmonary insufficiency, or metastatic malignancy may be expected to affect the urinary VMA levels, no interference has been observed following administration of tetracycline, isoproterenol, naphazoline, phenylephrine, ephedrine, digoxin, phenobarbital, and meperidine, some of which have caused difficulty with one or another of the tests for catecholamines (13). Similarly, neither uremia nor jaundice interfere with the test for VMA.

Although other semiquantitative tests (164, 170) have been devised for VMA determination, they thus far compare unfavorably as to simplicity of technique or instrumentation with the paper chromatographic procedure. This test also succeeds in demonstrating excessive excretion of 5-hydroxyindole acetic acid, a circumstance typical of the carcinoid syndrome (13). Bidirectional paper chromatography unfortunately is quite time consuming, and it would be difficult for a single technician to perform more than a few such determinations per day. On the other hand, a simple and rapid colorimetric test recently devised for the measurement of VMA in urine can easily permit twenty or more determinations by a single technician in a few hours (114). This screening test can be performed in any routine clinical laboratory and therefore may become widely available. Although many hundreds of such tests were carried out with but a single false negative and false positive result, the procedure required that the patients avoid coffee, fruit and vanilla prior to urine collection. Since failure to observe the dietary restrictions also led to false positive results, the test was recently modified (171). The latter can be performed upon random urine samples, the results being expressed as R values. A positive screening test for pheochromocytoma ( $R < 1.30$ ) requires a VMA determination by paper chromatography for confirmation.

Resection of a pheochromocytoma results in a return of previously high VMA excretion to normal levels. A number of patients with normal catecholamine but high VMA excretions have had pheochromocytomas removed (172). Moreover, Kraupp *et al.* described one patient with a pheochromocytoma who ex-



creted large amounts of VMA and catecholamines during paroxysms, but only increased VMA between paroxysms (173).

#### SUMMARY

Past inadequacy in detecting pheochromocytomas by clinical examination is self-evident.

At present, only accurate diagnosis stands between almost uniform surgical cure and the high mortality associated with this rare tumor. A means is now available for the inexpensive and rapid screening of patients for detection of pheochromocytomas. Since the urine VMA determination is unassociated with any discomfort or danger to the patient, only the frequency of negative tests may restrain the physician from its broad application. The data presented herein would appear to indicate that at least a urine VMA screening test be performed upon *all* patients with:

- a) *hypertension*;
- b) *paroxysmal episodes* (i.e., vasomotor attacks, vomiting, chest pain, abdominal pain, dyspnea, palpitations, convulsions, sweating, headaches and anxiety reactions);
- c) *hypermetabolic states* without clear-cut laboratory evidence of hyperthyroidism;
- d) *inappropriate response to mild trauma or anesthesia* (pressor or depressor);
- e) *neurocutaneous syndromes* (von Recklinghausen or von Hippel-Lindau).

A positive VMA screening test certainly requires either a semiquantitative VMA analysis or a catecholamine determination, or both. Should these chemical studies suggest the presence of a catecholamine secreting tumor, no more than careful chest x-rays, and perhaps abdominal flat films, pyelography and tomography should be attempted prior to the usual preparation for surgery. Even the abdominal x-rays cannot assist the surgeon appreciably, in view of the demonstrated need for routine anterior abdominal exploration in the majority of such patients.

The almost endless variation in the clinical appearance of pheochromocytoma has been but recently appreciated. It is hoped that increased clinical suspicion in conjunction with the newer diagnostic techniques may succeed in lowering the frequency with which this tumor is diagnosed only at autopsy.

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# RECOGNITION AND THERAPEUTIC IMPLICATIONS OF ALDOSTERONISM IN PATIENTS WITH ARTERIAL HYPERTENSION

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A relationship between salt metabolism and the pathogenesis of arterial hypertension has long been suspected, and it has been thought that a sodium-retaining hormone of the adrenal cortex was in some way involved in this relationship (1). Analysis of this interrelationship is difficult because the various forms of high blood pressure cannot be traced to the same cause and because the adrenal cortex is now known to secrete at least two different hormones, a situation which was not appreciated in earlier studies.

In the present discussion, the current status of our knowledge of the adrenal cortical hormones in their relation to regulation of blood pressure will be briefly considered, in order to provide a background for a review of the possible role of aldosterone in the various forms of human arterial hypertension. The implications of this information in the management of patients with high blood pressure will also be considered.

## ADRENAL CORTICAL HORMONES AND THEIR RELATION TO REGULATION OF BLOOD PRESSURE

Important work of the last two decades has revealed that the human adrenal cortex is the source of at least two endocrine secretions, hydrocortisone and aldosterone (2). These two hormones have different biological actions, and their rates of secretion are controlled by different trophic substances. As might be expected, the two hormones appear to influence the arterial blood pressure in different ways. In addition, the adrenal gland secretes a number of other steroids, the biological significance of which are not known (3).

The secretion of hydrocortisone is regulated by the specific trophic hormone, ACTH. The latter has a significant but apparently only a transient effect on the secretion of aldosterone, for which no specific trophic factor has as yet been identified. Changes in sodium and potassium balance and in the intravascular volume significantly influence the secretion rate of aldosterone (4), but the mechanisms by which these influences are exerted still need to be defined.

It is convenient to classify hydrocortisone and aldosterone and their derivatives according to their main biological activities as either glucocorticoids or mineralocorticoids. It should be recognized, however, that this classification is arbitrary and by no means absolute. In large dosage glucorticoids may resemble mineralocorticoids and vice versa. The term, glucocorticoid, is used to

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This work was supported by a grant from the United States Public Health Service (H-1275), by Mrs. Elizabeth H. Fleitas and by Mrs. Richard C. duPont.

describe the remarkable but poorly understood actions of hydrocortisone, or of corticosterone and their synthetic derivatives, which support gluconeogenesis, inhibit inflammation, modify capillary permeability and influence the distribution of electrolytes across cell membranes. Because of these actions hydrocortisone is essential for well-being and appears to play an important role in the reaction to various psychic or physical stresses. In contrast, the leading characteristic of mineralocorticoids is to stimulate sodium chloride reabsorption and potassium secretion by the renal tubule. Desoxycorticosterone and 11-desoxyhydrocortisone act in this way, but aldosterone is by far the most powerful of the natural mineralocorticoids. Mineralocorticoids also may have extra-renal actions, but these effects have not as yet been shown to be biologically significant.

Both the glucocorticoid- and mineralocorticoid-type hormones appear to be involved in blood pressure regulation; thus, adrenal insufficiency is regularly associated with hypotension which can be improved by either hydrocortisone or aldosterone. The supportive effect of hydrocortisone appears to be more immediate while that of aldosterone is delayed and may be a result of its effect on electrolyte balance.

Both glucocorticoid- and mineralocorticoid-type hormones when present in excess can produce hypertension both in man and in certain, but not all, species of experimental animals (3). Thus, excessive hydrocortisone secretion as in Cushing's syndrome, or excessive aldosterone output as in primary aldosteronism, are both accompanied by arterial hypertension. The nature of the pressor effects of these steroids is not clear. However, experimentally the hypertension produced by glucocorticoids such as hydrocortisone is relatively mild and is independent of dietary sodium intake. In contrast, hypertension produced by mineralocorticoids such as aldosterone or its longer known prototype, desoxycorticosterone, is slower to develop, more severe, and can be entirely prevented by deprivation of dietary sodium. It should be noted that the hypertension induced by aldosterone and other mineralocorticoids is also accompanied by the characteristic effects of these hormones on electrolyte metabolism, chiefly abnormal sodium retention, potassium depletion and extracellular alkalosis. The evidence seems to suggest, therefore, that the hypertensive effect of aldosterone is indirect and is a consequence of its effects on sodium and potassium balance.

#### THE ROLE OF ALDOSTERONE SECRETION IN VARIOUS FORMS OF HUMAN ARTERIAL HYPERTENSION

##### *Forms of Human Arterial Hypertension*

A number of classifications have been employed for the various forms of human arterial hypertension. These classifications have been largely descriptive, possibly because no definite biochemical abnormalities have been identified in any large proportion of these patients. In the present discussion, the following classification (5) will be employed:

In the large majority of patients no cause for arterial hypertension is known.

By definition this group has been termed primary or benign essential hypertension. Secondary hypertension refers to another group in which the high blood pressure is a consequence of other diseases. Various types of chronic renal disease probably comprise the most common cause of secondary hypertension, and it is often impossible to distinguish primary hypertension from hypertension, which is secondary to renal disease, because patients are not observed in the early uncomplicated stages of their illness.

Two rarely occurring types of secondary hypertension are noteworthy because they reveal pathophysiological mechanisms which may possibly play a role in other more common types of hypertension. Thus, following the classic studies of Goldblatt (6) in the dog, it has been recognized that in a very small fraction of patients, arterial hypertension is caused by impaired circulation to a kidney, and that this condition can be completely corrected by nephrectomy. In another small fraction of patients with high blood pressure, the disease has

TABLE I

*The Role of Aldosterone in Various Forms of Arterial Hypertension*

- A. Arterial Hypertensive Diseases Caused by or Associated with Hypersecretion of Aldosterone.
  1. Primary Aldosteronism due to Adrenal Adenoma
  2. Malignant Hypertension (without an Adrenal Tumor)
  3. Malignant or Severe Hypertension due to Unilateral Renal Disease
  4. Malignant or Severe Hypertension, Possibly ? due to Congenital Adrenal Hyperplasia
- B. Hypertensive Diseases Not Definitely or Regularly Accompanied by Hypersecretion of Aldosterone.
  1. Primary (Benign Essential) Hypertension?
  2. Primary Hypertension complicated by Renal or Cardiac Insufficiency
  3. Renal Hypertension?

been shown to be the result of excessive secretion of epinephrine or of norepinephrine (7) from a chromaffin-cell tumor, and this condition can be corrected by removal of the tumor.

Malignant hypertension refers to a syndrome characterized clinically by evidences of severe hypertension usually with papilledema and an accelerated course, and pathologically by necrotizing arteriolitis. This syndrome may develop *de novo* but usually occurs as a phase superimposed on antecedent hypertensive disease of some other type.

*Arterial Hypertensive Diseases which are Caused by or Regularly Associated with Hypersecretion of Aldosterone*

At the present time, four different clinical entities are recognized in which oversecretion of aldosterone is associated with arterial hypertension, that is, primary aldosteronism due to an adrenal adenoma, malignant hypertension, malignant or severe hypertension due to unilateral renal disease and severe or malignant hypertension which is possibly the result of congenital adrenal hyperplasia (see Table I). As might be expected, aldosterone hypersecretion in

any of these four disorders is usually associated with abnormalities in sodium and potassium balance.

*Primary Aldosteronism due to an Adrenal Adenoma.* The syndrome of primary aldosteronism is the effect of increased aldosterone secretion alone in a previously normal subject. Characteristically, this syndrome results from the autonomous, primary oversecretion of an adrenal adenoma, which produces a disorder, often long-standing, characterized by mild hypertension, sodium retention and potassium wastage. Edema is characteristically absent, and most of the symptoms such as polyuria, polydipsia and muscular weakness, can be traced to the potassium depletion. Thus, inability to form concentrated urine is related to potassium-depletion nephropathy. Removal of the adrenal tumor corrects the entire syndrome, although occasionally the blood pressure may not return to normal until several months after operation.

Since Conn first described this syndrome (8), over 35 cases have been reported in the literature (4), but Conn has personal knowledge of over one hundred such cases (3). Primary aldosteronism appears to be an exact metabolic counterpart of states which had previously been produced in animals by overdosage of desoxycorticosterone.

A much smaller number of cases have been reported in which this syndrome was considered to have been associated with bilateral adrenal hyperplasia. However, as will be discussed below, these cases have usually had severe hypertension of shorter duration, and the absence of adenoma suggests that the oversecretion may have been the result of some extra-adrenal stimulus.

Most recently, a small number of cases have been noted in children (10-12); these are characterized by potassium deficiency, hypokalemic alkalosis and retarded growth. Aldosterone hypersecretion is present, but is associated with bilateral adrenal hyperplasia, which suggests extra-adrenal, and perhaps a congenital disorder. These patients are also of special interest because they do not have arterial hypertension, a finding which further supports the idea that aldosterone itself is not necessarily a potent pressor agent, and also provides additional evidence for the proposal, to be amplified below, that the aldosteronism associated with severe or malignant hypertension is probably a secondary phenomenon.

Laboratory studies in primary aldosteronism reveal an increase in urinary aldosterone, or an increased rate of aldosterone secretion as determined indirectly by isotope dilution techniques (4). Potassium depletion is characteristic, usually with increased plasma bicarbonate and hypokalemia. Hypernatremia may be noted, and hypomagnesiumemia has also been reported (13). The cardinal metabolic abnormality is the tendency for potassium wastage in the presence of gross depletion of body potassium. It follows that these patients, perhaps unlike patients with hypokalemia from gastrointestinal or renal disease, tend to resist potassium repletion. Supplements of potassium stimulate more aldosterone secretion, which in turn increases potassium excretion; as a result, the potassium deficiency is unusually difficult to correct.

Diagnostically, the syndrome of primary aldosteronism must be distinguished



from other conditions also associated with potassium deficiency. The presence of extracellular acidosis eliminates renal tubular acidosis as a cause. However, patients with sodium-losing renal disease and hypokalemia may have a compensatory increase in aldosterone secretion. In these patients, observation on a low sodium diet may be necessary to demonstrate normal sodium conservation, which is present in primary aldosteronism but absent in the aldosteronism secondary to renal disease. Familial periodic paralysis, diabetes insipidus, as well as various other states of extracellular alkalosis, may at times also present problems of differentiation.

*Malignant Hypertension.* In this syndrome we have found that the secretion rate of aldosterone is very often significantly increased (9). Furthermore, a tendency to hypokalemic alkalosis is not unusual, and the overproduction of aldosterone is not readily modified by changes in the sodium content of the diet as it is in normal subjects and in patients with benign hypertension (14).

The cause of malignant hypertension is still unknown. Possibly aldosterone hypersecretion produces the syndrome in man as it does in animals. However, several lines of evidence suggests that the hyperaldosteronism of malignant hypertension is more likely to be either a secondary or an associated phenomenon because: (1) the disease state is clearly not the same as that of primary aldosteronism due to an adrenal adenoma; (2) adrenal adenomas are exceptional in malignant hypertension, and it therefore seems likely that the bilateral adrenal hypersecretion is triggered by some extra-adrenal mechanism; (3) adrenalectomy usually does not correct or improve the condition. While the failure of adrenalectomy in these cases could be due to irreversibility of the disease once it has become firmly established, our experience indicates that this is not the most likely explanation. Bilateral adrenalectomy in two of our cases has not only failed to arrest progress of the hypertension, but both patients have needed large maintenance doses of mineralocorticoids; (4) hyperaldosteronism is not regularly associated with most forms of hypertension and becomes evident only as complications and the malignant stage develop, suggesting that increased secretion of the hormone is itself a complicating rather than an initiating factor. However, even if hypersecretion of aldosterone is not a primary cause of the hypertension, it remains possible that hypersecretion of aldosterone may participate in causing or sustaining the malignant stage.

The search for a cause of hyperaldosteronism in malignant hypertension led us to examine the role of the kidneys (15, 16) because renal damage is such a predominant feature of this syndrome. A large body of experimental evidence, which has been reviewed (3), has shown that renin, a protein released from the ischemic kidney, causes the release of a pressor peptide, angiotensin, from a specific plasma globulin. Furthermore, it has been shown that administration of renin to the rat causes hypertrophy of the zona glomerulosa of the adrenal cortex which is the site of aldosterone formation. Also, renin, released by the rat kidney is suppressed by administration of mineralocorticoid or of salt, and is increased by salt deprivation or adrenalectomy. It therefore seemed possible that release of renin because of kidney damage, with many micro-occlusions

of the renal vessels, might account for the increased aldosterone secretion of malignant hypertension. This possibility has actually been demonstrated in a recent study which showed that the infusion of angiotensin consistently increases the secretion of aldosterone in normal subjects (15). Altogether, these observations are provocative because they point to the existence of a renal-adrenal interaction which may be involved in the pathogenesis of malignant hypertension. It now seems that there may be a mechanism which normally operates to sustain renal perfusion by promoting sodium conservation through stimulation of the adrenal cortex. This mechanism may become inappropriately overactive in malignant hypertension. Furthermore, it has been shown in animals (17) that the administration of mineralocorticoids together with renin leads to the production of severe vascular damage, an observation which may be significant in relation to the necrotizing arteriolitis of malignant hypertension.

However, much more work must be done before definitive statements can be made. Neither renin nor angiotensin have been unequivocally demonstrated in human plasma. It is thus possible that renin is not released by normal kidneys, and that, therefore, its effect on aldosterone secretion may be accidental or nonspecific. Nonetheless, the evidence to date directs increased attention toward definition and correction of the renal circulatory disorder in cases of malignant hypertension and suggests that increased dietary salt may even be a useful therapeutic measure.

These recent observations may explain why adrenalectomy is not helpful in treating hypertension; if a renal-adrenal interaction does exist, removal of the adrenals, or sodium deprivation, might permit an even greater release of the renal pressor substance, which might aggravate the disease. The participation of such a renal pressor substance in malignant hypertension also might account for the clinical and pathological differences (16) between this syndrome and that of primary aldosteronism, in which a renal factor is absent.

*Malignant or Severe Hypertension due to Unilateral Renal Disease.* Observations made by the newer techniques of renal arteriography and differential renal function suggest that unilateral renal disease may play a role in the causation of a much higher proportion of cases of hypertension than was previously thought (18). Various workers have noted that the hypertension associated with unilateral renal disease is at times severe or malignant (19), that the course may be accelerated, and that it may be accompanied by polyuria (20) and by hypokalemic alkalosis (21). More recent reports have indicated that hyperaldosteronism may also be observed in these patients (15, 22) and that nephrectomy or repair of the renal circulation may correct not only the excessive aldosterone secretion and alkalosis, but also the severe hypertension.

This condition is not easily diagnosed because demonstrable deformities in the renal vasculature may not be exactly related to functional abnormalities. Neither is it always possible to rule out some degree of damage in the second kidney. However, while Goldblatt (6) appears correct in generally connecting severe hypertension with bilateral constriction of the renal arteries, it seems clear that the syndrome of severe or malignant hypertension with increased

aldosterone secretion may be associated with certain instances of unilateral damage to the renal circulation. This condition may therefore be another, although unusual, clinical expression of Goldblatt hypertension, with renal ischemia leading to renin release and hyperaldosteronism.

Early diagnosis seems especially important in these cases because either a nephrectomy or repair of renal vessels may be curative. Both arteriography and differential renal function tests may be helpful, but are not always definitive. Measurement of aldosterone secretion may also prove useful in distinguishing these patients. If the hypertension is severe or malignant, a diagnosis of primary aldosteronism is unlikely, and attention may then be focused on searching for renal abnormalities. However, because of the diagnostic difficulties, until more definitive techniques have been developed it may sometimes be ultimately necessary to explore both adrenal glands and kidneys.

*Severe or Malignant Hypertension Possibly due to Congenital Adrenal Hyperplasia.* A small group of patients (23-30) have been tentatively separated from the other instances of severe or malignant hypertension. This distinction may not be justified, but is based partly on the fact that these patients are considerably younger than most patients with severe hypertension, and also because the condition appears to be somewhat improved or completely relieved by total or partial adrenalectomy. Adrenal adenomas are not found in these patients, and the adrenal glands have proved to be either normal or hyperplastic. Moran and associates (29) and Conn (3) have thought that they may represent a form of congenital adrenal hyperplasia, and Conn believes that polyuria of long duration is a diagnostic feature. However, according to our experience, they may not belong in a special group. Biochemical studies of adrenal steroid function have not so far distinguished them from other patients with malignant hypertension and aldosteronism; it remains possible, therefore, that the response of some of them to adrenalectomy is nonspecific. Thus, one of our patients (27), a nine year old boy, has retained his hypertension two years after adrenalectomy. Moreover, another, a girl of the same age, whose parents refused to permit operation, has improved considerably on medical treatment in the past two and one-half years (9).

It is, therefore, not yet certain that the adrenal hypersecretion plays a causal role in the hypertension of these patients, and longer experience with adrenalectomy is necessary before the operation can be recommended for this group.

#### HYPERTENSIVE DISEASE NOT DEFINITELY OR REGULARLY ASSOCIATED WITH ALDOSTERONISM

Aldosterone secretion does not appear to be regularly increased in the more common forms of arterial hypertension (Table I), and its role in these conditions is therefore more questionable. The use of isotope dilution techniques for measuring the rates of aldosterone secretion in patients with primary hypertension has revealed values similar to those of normal subjects (9). These measurements therefore indicate that aldosterone oversecretion is probably not involved in the pathogenesis of primary hypertension. In addition, these

patients do not have the abnormalities in electrolyte metabolism which are usually associated with aldosteronism.

The secretion rate of aldosterone, however, may at times be increased in hypertensive patients who have developed cardiac or renal complications (9). Further study of this group and of patients with renal disease without hypertension is required before these observations can be interpreted properly. Increase in aldosterone secretion in such patients may also be a sign that the malignant phase is to be expected.

Genest and his associates have reported (32) a statistically significant increase in the mean urinary excretion of aldosterone of 55 per cent of patients with essential, renal or malignant hypertension, and two other groups have obtained similar results. Genest has proposed that essential hypertension is mild chronic hyperaldosteronism (33).

Further study may resolve the differences between the results obtained from study of secretory rates as opposed to results based on excretory rates. Ultimately, measurements of the circulating blood level of the hormone may be necessary. However, it should be pointed out that a number of objections can be raised to the studies based on the measurement of urinary excretion of the hormone. First, only a very small fraction of the aldosterone secreted by the adrenals is excreted unchanged in the urine. Changes in this small fraction may not reflect gross changes in adrenal secretion and could be the result of altered metabolism of the hormone. Second, the techniques thus far employed to measure this small fraction are difficult and are subject to losses during the procedure for which no correction has been made. Third, the rate of aldosterone secretion, unlike that of all other hormones, fluctuates widely, depending on the electrolyte balance; therefore rigid control of this factor is necessary because large changes can occur as a result of physiological rather than pathological factors. Fourth, the common forms of hypertension may not be homogeneous either in etiology or in the extent to which occult complications may be present, as in kidneys and heart. Therefore, general conclusions drawn from averaging aldosterone measurements obtained from groups of these patients may not be justified. Nonetheless, it remains possible that the increased urinary excretion of acid-liberated hormone is a true reflection of a biologically significant abnormality which is present in some patients with benign hypertension. Further study is necessary in order to define more precisely the normal ranges and to compare simultaneously secretory and excretory rates. However, it is the author's view that aldosterone hypersecretion does not participate in the pathogenesis of the more common forms of arterial hypertension. Accordingly, when aldosteronism occurs in such patients it is likely that it is secondary to renal or cardiac disorders, and treatment should be aimed towards correction of these complicating situations.

#### SUMMARY

1. In certain, but not all experimental animals, administration of mineralocorticoids such as aldosterone, which primarily influence electrolyte balance,



produces arterial hypertension. This hypertension is dependent on the presence of adequate sodium in the diet and is accompanied by potassium depletion and extracellular alkalosis.

2. Primary aldosteronism in man represents the naturally occurring expression of excessive aldosterone secretion in a normal subject. A syndrome characterized by potassium wastage and mild hypertension develops and can be entirely corrected by removal of the adrenal tumor. Recent experience, however, suggests that primary oversecretion of aldosterone in children may not always be accompanied by hypertension.

3. Increased secretion of aldosterone is also very often associated with two, or possibly three, forms of hypertensive disease: malignant hypertension, severe or malignant hypertension due to unilateral renal disease, and severe hypertension possibly due to adrenal hyperplasia. The increased aldosterone secretion in these patients is considered a secondary phenomenon. Proper diagnosis is of special importance because nephrectomy, if the cause is unilateral renal disease, may be curative. Adrenalectomy may be of value in the group whose hypertension is tentatively classified as due to congenital adrenal hyperplasia; however, in malignant hypertension the procedure does not appear to be particularly helpful.

4. The evidence presented suggests that the increased aldosterone secretion in patients with severe hypertension may be a consequence of the release of a pressor substance, angiotensin, by renin which is released by the ischemic or damaged kidney. Angiotensin in turn has been shown to stimulate the secretion of aldosterone. Whether such a renal-adrenal interaction participates in regulation of sodium balance in normal subjects remains to be established.

5. Aldosterone overactivity has also been implicated in the common forms of arterial hypertension including primary (essential) hypertension. The studies which support this view have been based on measurement of excretion rather than secretion. It is the author's view, based on secretion rate studies, that abnormal aldosterone secretion is not a part of uncomplicated primary hypertension. However, further investigation may be necessary in order to define more precisely the normal ranges of aldosterone secretion and to compare secretory and excretory rates obtained simultaneously.

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## THE DRUG TREATMENT OF HYPERTENSION

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Although there is almost general agreement that antihypertensive drugs prolong the life of patients with the accelerated form of hypertension, there has been no unanimity of opinion as to their efficacy in subjects with primary hypertension (1-6). Reports have appeared which indicate that antihypertensive drugs ameliorate the signs and symptoms of primary hypertension, modify some of the complications of the disease and even prolong survival (5, 7-21). The issue, however, is not definitely resolved and the analysis of additional large series of patients should help to clarify the question of the efficacy of antihypertensive drug treatment in primary hypertension. The present study is an evaluation of the response to antihypertensive drug treatment in patients with primary and secondary hypertension over a period of three years.

### METHODS

One hundred sixty-seven patients in the hypertension outpatient clinic were studied. All of the subjects had documented hypertension for at least six months before their inclusion in the study group. One hundred fifty-two subjects were under treatment for primary hypertension and fifteen were treated for hypertension associated with either: chronic glomerulonephritis or chronic pyelonephritis or renal artery obstruction. All of the patients were examined at intervals of several weeks by physicians who were unaware of the study program. The cases included in the study comprised all of the patients in the clinic from June 1957 to June 1960 (three years).

The antihypertensive drugs used in the study included:

- (a) Rauwolfia serpentina derivatives: reserpine, whole root of Rauwolfia serpentina, syrosingopine and Su 3118 (Ciba).
- (b) Oral diuretics: chlorothiazide, hydrochlorothiazide, benzydoflumethiazide, triethlormethiazide and chlorthalidone.
- (c) Ganglion-blocking agents: pentolinium, mecamylamine and trimethidinium.
- (d) Hydralazine.
- (e) Guanethidine and bretylium tosylate.

The drugs were administered either singly or in combination. All medications were administered by mouth and the dosage was adjusted until the desired therapeutic effect was achieved or toxic symptoms appeared. The period of

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Aided by grants from the National Heart Institute [H-A-4477, H-1164(CS)] and the American Heart Association.



treatment with each combination of drugs varied from six weeks to three years. The total time each patient was under treatment varied from 6 weeks to 7 years with a mean period of observation of 11 months.

The patients were classified into three groups designated "mild", "moderate" and "severe". The mild group was composed of patients with persistent blood pressures above 150 mm Hg systolic and 100 mm Hg diastolic without evidence of organ involvement attributable to hypertensive disease. The severe group was composed of patients with systolic blood pressures above 190 mm Hg and diastolic blood pressures above 120 mm Hg with involvement of two or more organs such as the heart, kidney, brain or eye. The moderate group was composed of patients with criteria intermediate between mild and severe.

The patients were also separated into three groups, "good", "fair" and "poor", depending on their response to the antihypertensive drugs. A good response was

TABLE I  
*Results of Treatment in 152 Subjects with Primary Hypertension*

Severity of Hypertension	Treatment Results			Total Number of Patients
	Good	Fair	Poor	
	No. of Patients			
Mild	15	4	1	20
Moderate	23	12	12	47
Severe	30	25	30	85
Total	68	41	43	152
Per cent				
Total	45	27	28	100

registered when there was a decline in the blood pressure to normal or near normal values together with regression of organ involvement when present. A poor response was no decline or an equivocal change in the blood pressure with no regression of organ involvement when present. A fair response was intermediate between good and poor responses.

#### RESULTS

Table I summarizes the results of treatment in patients with primary hypertension. A good response was recorded with at least one antihypertensive drug or combination of antihypertensive drugs in 45 per cent of all patients with primary hypertension. Furthermore, 72 per cent of these patients had either a good or fair response. It is apparent from Table I that the highest percentage of good responses was observed in patients with mild primary hypertension and that as the severity of the disease increased the good treatment results de-

creased. Similarly, the highest percentage of poor treatment results was observed in the patients with severe primary hypertension. Table II summarizes the results of treatment in the fifteen patients with secondary hypertension and demonstrates that the results of treatment were not as encouraging as in patients with primary hypertension.

A total of 458 antihypertensive regimens were employed in the 152 patients with primary hypertension. A good response was elicited in only 28 per cent of these therapeutic trials and a good to fair response was observed in 55 per cent of the tests. A good response was recorded in only  $\frac{1}{10}$  of the 52 therapeutic regimens in the 15 secondary hypertensive patients and a good or fair response was registered in about  $\frac{2}{5}$  of these therapies.

Each of the antihypertensive drugs was usually given until the desired therapeutic result was achieved or side effects appeared. Consequently many side

TABLE II  
*Results of Treatment in 15 Subjects with Secondary Hypertension*

Severity of Hypertension	Treatment Results			Total Number of Patients
	Good	Fair	Poor	
	No. of Patients			
Mild	1	0	0	1
Moderate	0	4	0	4
Severe	2	1	7	10
Total	3	5	7	15

actions were observed. Mental depression, nasal stuffiness and occasional abdominal discomfort were sometimes seen during treatment with the *Rauwolfia serpentina* derivatives; hypokalemia was not infrequent when the patients were given oral diuretics; constipation and visual disturbances were recorded in patients treated with the ganglioplegic drugs; and diarrhea, muscular weakness and nasal congestion were observed in patients under treatment with guanethidine and bretylium tosylate. The syndrome resembling disseminated lupus erythematosus was not seen in the small number of cases treated with hydralazine. Postural hypotension was observed in many cases, especially in those patients treated with ganglion blocking or postganglionic sympathetic nerve blocking drugs.

#### DISCUSSION

This study indicates that antihypertensive drug therapy is efficacious in reducing the blood pressure and in diminishing the signs and symptoms of organ involvement in primary hypertension. In the present series a good result is observed in 45 per cent of the cases. This may be compared to a good result of 42 per cent in the previous series from the same clinic which evaluated a total

of 116 patients over the prior 3½ year period (18). The saluretic drugs and those acting at the nerve-arteriole junction (guanethidine and bretylium tosylate), are the two groups of drugs which were unavailable at the time of the previous communication (22, 23). The veratrum derivatives were not used in the present series. A total of 72 per cent of the cases in the present study had either a good or fair response. These figures indicate that there has been a small, but definite improvement in the percentage of cases of primary hypertension successfully treated during the past three years. This improvement may be expected to increase since some of the newer drugs have not been in use throughout the entire three year period.

Although a good result may be achieved in 45 per cent and a good to fair result may be obtained in 72 per cent of all cases of primary hypertension, only 28 per cent of all the combinations of drugs employed in these patients yielded a good result and 55 per cent yielded either a good to fair result. These figures indicate that although the treatment of primary hypertensive cases is slowly becoming more successful, a large number of trials of different drugs are needed in order to achieve these results. It is presumed that the less efficacious drugs will gradually fall into disuse. In this as in the previous series, the highest percentage of good results of treatment was obtained in the mild group of subjects with primary hypertension (15, 18). These findings tend to support the case for drug treatment of primary hypertension as early as possible in the course of the disease.

#### SUMMARY

1. The response to antihypertensive drug treatment was evaluated in 167 patients with primary and secondary hypertension.

2. Either a good or fair treatment response was recorded in 72 per cent of the cases of primary hypertension. A good or fair treatment result was obtained in 55 per cent of the 458 antihypertensive regimens employed.

3. The results tend to support the efficacy of early treatment of primary hypertension.

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## HYPERTENSION IN CHILDHOOD

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Hypertension in childhood is almost always due to a specific and detectable cause. Renal disease, predominantly acute and chronic glomerulonephritis, accounts for most cases of hypertension seen in pediatric practice; less commonly pyelonephritis, especially in relation to congenital abnormalities of the kidney, or disturbances of renal blood supply, will be found. Coarctation of the aorta, although rare, is much commoner than tumors of the adrenal cortex or medulla as an etiological factor in childhood hypertension. Central nervous system disturbances and lead or mercury poisoning may present as hypertension syndromes in the young. Rare cases have been described which appear to fall in the category of essential hypertension of adult life (1).

The suspicion of hypertension and the differential diagnosis of the specific etiology are developed by careful anamnesis and physical examination. A history of repeated episodes of urinary tract infection, particularly in a male child, should alert the physician to a diagnosis of pyelonephritis. The clinical diagnosis of glomerulonephritis rarely gives difficulty, but it must be remembered that hypertension produced by other causes may damage the kidneys and show urinary abnormalities.

Because hypertension is rare in childhood, it is seldom considered in a differential diagnosis. Yet diverse symptoms such as headache, mental changes, visual disturbances, nausea, vomiting and abdominal pain may all be manifestations of hypertension. In addition to obvious urinary symptoms such as frequency, polyuria and nocturia, bouts of fever and failure to grow and develop normally must raise the suspicion of renal disease or hypertension. Despite its rarity, lead ingestion should be sought in order to obviate complicated investigation and afford specific and effective medical therapy. A family history of hypertension, or the presence or absence of renal or other congenital abnormalities cannot be overlooked. The history may not be diagnostic or suspicious of hypertension, therefore blood pressure measurement must be an integral part of the physical examination of every child.

It is surprising how seldom a blood pressure measurement is made in the young patient whose physical examination is otherwise most complete. Several of the cases to be described in detail had had no blood pressure measurement during long periods of illness, and in two it was not done until the finding of papilledema led to consultation with a neurologist.

Blood pressure in children is measured in the conventional manner with the antecubital fossa held at approximately the level of the heart and diastolic pres-

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sure read at the last audible sound. The diastolic pressure in young children is often difficult to measure and may be unobtainable in children under seven years of age. Occasionally systolic pressure can only be obtained by palpation. A small cuff 9 centimeters in width should be used for children up to seven years of age. Above this age the adult cuff is usually satisfactory. Blood pressure is quite low in the newborn period, but at the age of one month a systolic reading of about 80 mm Hg may be expected. Up to the age of ten years systolic pressures range from 90 to 100 mm Hg and diastolic readings from 60 to 70 mm Hg. Slight rises toward the customary young adult levels start in the second decade, especially during puberty and adolescence. In a study of over 19,000 children under the age of fifteen, a diastolic pressure over 90 was found in only three instances (2).

Detection of hypertension should immediately raise the possibility of coarctation of the aorta. The likelihood of finding a coarctation is much greater in childhood hypertension than among adults in whom large numbers of patients with essential hypertension have diluted the incidence of coarctation. Once suspected, this diagnosis should be readily confirmed by palpation of the femoral pulses and comparison of arm and leg blood pressures. In children, the leg blood pressure is readily determined by placing the child on his abdomen and winding an adult-size cuff around the thigh with the rubber bag covering the antero-medial aspect of the thigh. The stethoscope is placed in the popliteal area. Systolic pressure is often more easily measured than diastolic. If the sounds are not well heard, the cuff may be wrapped about the calf and a systolic level measured by palpation of the dorsalis pedis pulse. The hypertension of coarctation exists only in the upper part of the body in the heart, head and arms, and low blood pressure is found in the legs. This is in marked contrast to normal subjects or other hypertensive patients in whom the blood pressure is higher in the leg than in the arm. Of 22 patients with coarctation 18 years of age or younger (17 were ten years or younger), femoral pulses were faint in three and not palpable in 19; blood pressure in the leg was either entirely unobtainable or lower than that in the arm (3). It is of interest that renal insufficiency does not occur in coarctation, presumably because the kidneys are in an area of low blood pressure and are protected mechanically by the coarctation from the effects of hypertension on the arterioles. Unusual location of coarctation or other major arterial constriction may be revealed by detection of a bruit over the involved vessel; in the small child careful auscultation of back, neck and abdomen may be more rewarding than in the heavily padded adult.

Diagnostic possibilities raised by the history and physical examination require laboratory and radiological confirmation. A careful examination of the urinary sediment is essential and gives information not otherwise obtainable. Unless a definitive diagnosis has been made by these methods, urological investigation is indicated in every case, starting with the intravenous pyelogram.

The intravenous pyelogram is customarily used to delineate renal anatomy and, in a broad sense, renal function. Congenital anomalies, ectopic location, favor pyelonephritis; poor dye concentration or excretion indicates poor renal function. Unexplained disparity in kidney size or function may indicate disease

of the artery to that kidney (4). Since the time of first appearance of dye in the renal pelvis is a measure of renal blood flow as well as urine formation, we have found it useful to take the first film of the intravenous pyelogram earlier than the customary five minutes after dye injection. In adults we now perform our intravenous pyelogram so that the dye is injected intravenously over a two minute period and the first film is taken three minutes after completion of the injection. Subsequent films are taken at 5, 7, 10 and 15 minutes after completion of the injection. A delay in the appearance of dye on one side, particularly when the dye shadow is denser and more persistent on the late side,\* has focused our attention upon seven (adult) cases of hypertension who were found to have renal artery stenosis by aortography (5).

In children because of their small size and hence more rapid blood flow, it might be desirable to take the first film at the conclusion of the dye injection and the next, two or three minutes later.

It should be emphasized that simultaneous early appearance of dye does not eliminate the possibility of renal artery stenosis. Obviously the presence of intrarenal or ureteral obstructive disease will allow no inferences concerning dye appearance time and renal artery disease. If no other etiology can be established, only aortography can rule out renal artery disease.

Two types of hypertension first demonstrated etiologically in animals have their human counterparts. Examples of renal artery stenosis, true Goldblatt kidney, are being recognized with increasing frequency and occur even in children (4, 6). Similarly Page's experiment (7) in which cellophane perinephritis produced hypertension in the rat, is reproduced in man with perinephric inflammation or hemorrhage (as in one of our cases).

Tumors of the adrenal glands are very rare causes of hypertension even in adults. Pheochromocytoma should be suspected particularly when the hypertension is episodic or there is evidence of hypermetabolism. Pharmacologic tests with antagonists of epinephrine and norepinephrine have been amply reviewed (8, 9). The importance of avoiding other medication (such as sedatives, Rauwolfia and antihistamines) which may give false positives must be borne in mind. Quantitative urinary excretion of catechol amines or of a metabolic end-product, vanillyl mandelic acid, (10) should be done when there is reasonable clinical suspicion of a pheochromocytoma. Aldosterone-producing tumor as a cause of hypertension has not yet been described in childhood. A hypochloremic, hypokalemic alkalosis, inability to concentrate the urine above 1.010, polyuria, muscle weakness, thirst and dryness of the throat in association with hypertension would point strongly to this diagnosis. One patient has been described with increased amounts of aldosterone in the urine, but without an adrenal tumor. This child was treated by adrenalectomy (11). The finding of amounts of aldosterone greater than normal in certain patients with severe hypertensive disease complicates the diagnosis of hypertension secondary to aldosteronism (12).

\*On the side of the stenosis the urine is often more concentrated and flows more slowly. Hence a denser and a more persistent shadow is observed because the scanty flow fails to wash the renal pelvis free of excreted dye.

Finally, there appear to be a small number of cases of hypertension in childhood which have been diagnosed as essential hypertension, the disorder responsible for most hypertension in adult life. Some of Nadas' (1) cases (4 out of 9) resemble essential hypertension of adult life closely in that other etiologies are thoroughly excluded, the blood pressure is only moderately elevated, is unassociated with evidence of renal damage and fairly well tolerated for a number of years. Among the patients so labeled, only a small number have been thoroughly investigated with such diagnostic steps as renal biopsy and aortography to exclude all known etiologies. These last measures, too, are not always as definitively exclusive as desired. For example, an aortogram taken in the posterior-anterior position may show an apparent normal renal artery arising from the aorta. Yet if the renal artery origin is covered by the breadth of the aortic shadow, an oblique view may be necessary to afford an unobstructed picture of the renal artery take-off, which may then appear constricted. Even renal biopsy, customarily done on one side, may miss a case of unilateral pyelonephritis, if there is no decrease in kidney size or alteration in pelvic architecture to suggest renal biopsy on the appropriate side.

#### TREATMENT

Establishment of a specific diagnosis will often lead to specific and sometimes curative treatment; in other instances, as with bilateral renal disease or in the rare case when no specific diagnosis can be made, empirical antihypertensive therapy, following principles established in treating adult hypertension, may afford striking results.

The cases to be described are chosen because of their extreme interest and to illustrate the management of the diagnostic problem and the long-term control of hypertension in children with hypotensive drugs.

#### *CASE I. Severe hypertension due to congenital bladder neck obstruction with hydronephrosis and chronic pyelonephritis*

A 9 year old girl was admitted to the Long Island Jewish Hospital in January 1956 because of headache, vomiting and abdominal pain. At the age of two years the child was seen at another hospital because of a urinary tract infection. Pus cells were found in the urine and she responded satisfactorily to aureomycin. Follow-up urine examinations were said to have been negative. The child grew more slowly than two older siblings and, although the parents brought this to the physician's attention, no investigation was made. Several years before admission, nocturia appeared three to four times a night. During the six months before entry, poor appetite, a craving for salt and a five pound weight loss were noted by the mother. The school and family physician detected a cardiac murmur and a chest x-ray and electrocardiogram were obtained. The latter showed left axis deviation but no cardiac enlargement was reported. During all this time the child's blood pressure was never measured. Finally, after three months of almost daily headache, vomiting and abdominal pain, she was hospitalized. On the day before admission she noted blurred vision. She had been a premature baby weighing five pounds at birth, but early development was normal. The family history was unremarkable. Two older siblings were well.

She appeared quite small for her age, weighing only 37 pounds and being 45 inches tall. Her complexion was pallid. Initial blood pressure readings were 190-208/148-158 in the arms, and 190/150 in the legs. The femoral pulses were palpable. Her optic fundi showed only narrowing of the arteries. The lungs were clear. The heart was not enlarged but there was a



moderately loud precordial systolic murmur. The aortic second sound was accentuated. The abdomen appeared distended in the bladder region and there was tenderness over the right kidney area. Abdominal pain was relieved on emptying the bladder.

Her urine contained 35 wbc/hpf with clumps; the specific gravity was 1.003 to 1.010. There was 4+ proteinuria. The hemoglobin was 10 Gm, rbc 3.0 M. The bun was 21 mg per 100 ml, serum CO<sub>2</sub> 24, Na 143, Cl 108, K 3.9 mEq/L. Serum calcium was 8.6 mg, phosphorus 3.6 mg and creatinine 1.0 mg per 100 ml. The urea clearance was 50 per cent of normal. Urine culture revealed proteus and enterococcus organisms. ECG showed the pattern of left ventricular hypertrophy. X-ray examination showed a bone age of only seven and one-half years. There was enlargement of the left ventricle. The intravenous pyelogram demonstrated poor visualization of the pelvis with diffusely distended calyces and lower ureters. Cystoscopy and retrograde pyelography demonstrated bilateral hydronephrosis, hydro-ureter and a distended bladder with vesicle neck obstruction.

### *Clinical Course*

The presence of fever, pyuria and bladder neck obstruction prompted the use of an indwelling Foley catheter and broad-spectrum antibiotics (tetracycline and later Furadantin and chloramphenicol). Administration of reserpine resulted in blood pressure levels as low as 135/118 mm Hg. Two weeks after admission she was afebrile, blood pressure averaged 180/120 and a transurethral resection of a hypertrophied (congenital) bladder neck was performed. Following this procedure protoveratrine, mecamlamine and reserpine were used to control hypertension. Erratic control was achieved, 160/120 being the usual range, but high levels of 200/160 and low levels of 130/100 were noted. The day before discharge her average blood pressure was 150/110 while taking mecamlamine 25 mg, reserpine 1.5 mg and protoveratrine 1.2 mg in three divided daily doses.

The child's mother was instructed in the technique of measuring blood pressure and she was given a stethoscope and sphygmomanometer. She then began to record the child's blood pressure four times daily, and except for occasional lapses due to trips, etc., has continued this record keeping for over four years.

By September 1956 the child was receiving 0.25 mg of reserpine three times daily and 50 to 80 mg of mecamlamine in three divided doses plus protoveratrine 0.4–0.5 mg three times daily. It was already apparent that this child required very high doses of ganglionic blocking drug, in excess of that ordinarily used for adults. She had had one severe episode of vomiting from protoveratrine in July 1956; it was omitted three months later. Blood pressure control was erratic. Frequent morning readings were almost normal, but marked hypertension was again present by evening. Typical blood pressure records were:

April 7, 1956	September 25, 1956
8 AM 138/76	10 AM 120/92
10 AM 118/76	1 PM 190/150
12 Noon 160/100	6 PM 194/160
2 PM 156/80	8:30 PM 200/160
6 PM 184/120	
8 PM 194/120	

The patient also received urecholine to overcome the adverse effects of ganglionic blockade on bladder emptying, and mandelamine for the chronic urinary tract infection. Her residual urine was 8 ounces. In October 1956 hydralazine was added in gradually increasing amounts to a maximum of 210 mg (in three divided doses) daily. The ensuing year brought many more normotensive blood pressure readings, for example on March 16, 1957, her blood pressure through the day was 96/70, 114/86, 112/80, 152/120, 172/148. The child had begun to grow and by October 1957 weighed 50 pounds and was 50 inches tall. Blood pressure readings on arising were now often so low that the morning dose of mecamlamine could be omitted, but control was so erratic that daily doses of mecamlamine varied from 0 to 80 mg. Residual

urine in August 1957 was 3¾ ounces. An important change occurred in January 1958 with the institution of therapy with chlorothiazide. It became possible to reduce the dose of mecamlamine on the average to only 5 mg three times daily and hydralazine was omitted. The very high evening diastolic readings which had been unremitting began to yield. On February 4, 1958, the blood pressures were 120-144/90-110, and on June 7, 1958, 104-132/72-96.

Since one of us (M.K.) had noted earlier that Marsilid was an effective hypotensive agent in some of our resistant adult hypertensives, this drug was added in March 1958 in a dose of 12.5 mg twice daily. The urinary residual was only 15 ml and the patient was now 52½ inches tall and weighed 57 pounds.

During the early part of 1959 there was frequent need to adjust the dose of mecamlamine. On some days the child's blood pressure was so well controlled that no ganglionic blocker was necessary; on other days up to 30 mg was necessary. Urea clearance was now 86 per cent of normal but urinary protein and pyuria were still present. The BUN was normal (14 mg%) but the intravenous pyelogram still showed persistent marked calyceal dilatation. In April 1959 blood pressure records of 120/96, 116/90 and 130/100 throughout the day were common. By late 1959 the marked swings of blood pressure were less apparent and by October 1959 (with blood pressures of 100-140/60-90, visits to the Outpatient Department were reduced to once every three months. Her weight was 83 pounds and height 56 inches. In August 1960, her blood pressures were 100-134/74-80 erect or supine. Her current medication schedule is:

Mandelamine, 0.6 Gm three times daily  
Urecholine, 5 mg three times daily  
reserpine, 0.5 mg daily  
iproniazide, 25 mg daily  
pyridoxine,\* 25 mg daily  
chlorothiazide, 0.25 Gm three times daily  
mecamlamine, 0-10 mg daily

Her optic fundi are entirely normal. ECG shows tall waves over the left ventricle. The cardiac silhouette still suggests an enlarged left ventricle. As it became obvious that the originally bad prognosis had been altered, necessary orthodontia has been carried out. The child is now entering puberty, attending school and leading a normal life.

#### *Comment*

The eventual outcome of this case is still in doubt, but a number of aspects may be justifiably emphasized. A disease state with a hitherto uniformly poor prognosis, in our experience, of six months or less, has been moderated so that almost five years have elapsed. During this time renal function has not deteriorated; it is as good as or better than it was in January 1956. The child's blood pressure is always normotensive on doses of medication far less than were only partly efficacious at the onset of treatment. The combination of drugs appears to have had advantages in the empirical reduction of blood pressure; the more normal the blood pressure readings achieved, the less hypotensive medication has been required. Although chronic pyelonephritis still persists, control of blood pressure (and presumably therefore of its sequelae) has been possible.

We believe the results in this case would not have been possible a decade ago and in this instance they are largely the result of the cooperation of an intelligent mother who had no previous medical training. She kept the daily record of blood pressure and drug administration and became familiar with the drugs by

\* To counteract possible toxic effects of iproniazide.

name and properties, so that she learned how to adjust doses of the ganglionic blocking agent to the previous blood pressure reading.

This case certainly emphasizes the need for a definitive diagnostic investigation in cases of pyelonephritis early in life. An intravenous pyelogram at the age of two rather than nine might have prevented permanent kidney damage. Failure to grow normally may be the only overt sign of a chronic illness such as severe pyelonephritis and hypertension. Failure to measure the child's blood pressure despite a cardiac murmur and left axis deviation on ECG and many other significant symptoms led to needless delay in making the diagnosis of hypertension.

*CASE 2: Accelerated hypertension due to congenitally hypoplastic kidney  
with segmental pyelonephritis*

A 12 year old white girl was admitted to the Long Island Jewish Hospital on November 18, 1959, because of blurred vision of two weeks duration. She had been active and feeling quite well otherwise. There had been no episodes of back or flank pain, and no urinary symptoms. The day before admission she was seen by an ophthalmologist who observed bilateral papilledema and referred the child to a neurologist. He was the first physician to measure her blood pressure. It was markedly elevated. Two years before she had had a two month period of severe daily morning headaches associated with occasional brief periods of fever to 102°. Blood tests and urine examination at that time were said to have been negative. During the year prior to admission the patient suffered from nosebleeds of increasing frequency.

Past medical history, growth and development had been normal. The family history was of interest in that both grandmothers had hypertension and died of strokes; the maternal grandfather had "hardening of the arteries" and died in his forties; one aunt had a nephrectomy for "back pain and infections" and another aunt had "nephrosis".

Physical examination revealed a well developed and nourished girl. Blood pressure in the right arm was 260/180 and in the left 230/170 mm Hg; it was higher in the legs. Ophthalmoscopy revealed a grade IV retinopathy with gross papilledema, hemorrhages, exudates and marked arteriolar narrowing and arteriovenous compressions. The heart was somewhat enlarged to percussion. There was a regular sinus tachycardia with a rate of 100. A mild systolic murmur was heard at the apex. A<sub>2</sub> was markedly accentuated. The abdomen was soft and nontender. The left kidney was palpable; the right was not felt. The remainder of the examination was normal.

*Laboratory Data:* Hg was 10.8 Gm, hematocrit 32% and wbc 12,750. Urinalysis showed 1 to 4<sup>+</sup> proteinuria, specific gravity 1.013-1.020. Sugar was absent. The sediment contained 8-10 RBC and 10-20 wbc with clumps per high power field. BUN was 18 mg%, cholesterol 270 mg% and glucose 103 mg per 100 ml, serum Na 148, K 3.5, Cl 104 mEq/L. An ECG showed characteristic changes of left ventricular hypertrophy. X-ray of the chest demonstrated concentric hypertrophy of the left ventricle with moderate dilatation of the aorta. Intravenous pyelogram showed a normal left urinary tract, the left kidney being larger than usual. The right kidney appeared quite small with considerable deformity of the pelvis and calyces. A phentolamine test was negative.

*Clinical Course*

On oral reserpine and bed rest there was a fall in blood pressure to 130/100. However, the child became quite drowsy and developed a spiking fever to 106°. Urine culture yielded *E. Coli*; a blood culture grew *staphylococcus aureus* and she was given chloramycetin. Tenderness in the abdomen over the region of the right kidney appeared. A diagnosis was

made of acute and chronic pyelonephritis in an atrophic shrunken kidney with superimposed accelerated phase of hypertension due to unilateral renal disease, and on November 25, 1959 an operation was performed. The right kidney was found to be hypoplastic with small vessels at its pedicle and it was removed. Postoperatively the child's blood pressure remained at 130/100 without hypotensive medication. Her fever subsided after the nephrectomy but recurred on the fourth postoperative day. On the addition of Furadantin® to her therapy her temperature became normal again. She was discharged on the 16th postoperative day with the urine free of albumin and formed elements.

The removed kidney weighed only 30 Gm. The upper two-thirds of the kidney, although small, appeared grossly normal with well defined medulla and cortex. The lower one-third showed complete loss of normal architecture: the lower calyx was dilated and its mucosa had a hemorrhagic granular appearance. Microscopic examination of this portion of the kidney showed marked scarring with many fibrotic glomeruli, interstitial fibrosis and diffuse round cell infiltration of the stroma. The tubules in this area were markedly dilated and filled with inspissated secretion. The vasculature throughout this kidney revealed proliferative intimal thickening with narrowing of the lumens. In some vessels in the lower pole the lumens were completely occluded. The pathological diagnosis was hypoplastic kidney with chronic pyelonephritis and arteriolonephrosclerosis.

In the ten month period since discharge, her blood pressure measured at home by her mother was 120-130/90-100 without medication. On syrosingopine (1 mg twice daily) the values were lower, 110-120/70-90 mm Hg. The optic fundi have shown remarkable improvement. All traces of the papilledema, hemorrhages and exudates have vanished. The arterioles still show a mild degree of narrowing. The cardiac silhouette has not changed in size. The urine is consistently free of albumin, red cells and white cells. The most recent BUN was 18 mg per 100 ml.

### *Comment*

In this child a congenitally hypoplastic kidney became the seat of severe but localized pyelonephritis with much interstitial scarring and gross destruction of normal renal architecture. This resulted in severe hypertension and grade IV retinopathy which led to a diagnostic study. The duration of the disease before nephrectomy can be estimated at two years on the basis of a history of headaches. Again, failure to measure blood pressure at that time makes it difficult to date the onset of disease and probably resulted in delay in establishing a diagnosis. Definitive surgical therapy by nephrectomy was employed and the accelerated phase of hypertension reversed. Blood pressure is almost normal ten months later and can be maintained entirely in the normal range with a small dose of Rauwolfia alkaloid.

### *CASE 3: Hypertension secondary to obscure renal disease*

An 11 year old boy was admitted to the Long Island Jewish Hospital on May 21, 1960, because of headache and vomiting of one years duration. The patient was in good health until May of 1959 when morning headaches associated with nausea and vomiting began to appear about once weekly. In December 1959 and again in April 1960 a left peripheral facial weakness appeared and slowly cleared. In April 1960 he was admitted to another hospital where skull x-rays and lumbar puncture were performed. A blood pressure measurement was not made. Two weeks before admission here he was seen by an ophthalmologist and by a family physician, neither of whom measured his blood pressure, but referred him to a neurosurgeon who detected hypertension for the first time. The child's birth and development were normal. His family history was not contributory.

He was a well developed and nourished boy who did not appear very ill. He was hyperactive



and his speech was minimally slurred. The blood pressure in both arms was 160/120 mm Hg and in the legs was 230/140 mm Hg. The heart appeared somewhat enlarged to the left. The second aortic and pulmonic sounds were both very sharp and loud. There was a grade II systolic murmur at the base and at the left sternal border. There was a slight residual left peripheral facial palsy. The optic fundi showed narrowed arterioles and scattered yellowish-white exudate. There were a few fresh and old hemorrhages in the left fundus. An ophthalmologist thought that the fundal appearance was more suggestive of periarteritis nodosa than simple hypertensive retinopathy.

*Laboratory examinations:* Urinalysis showed a trace to 2+ protein, but proteinuria was no longer found after the first two weeks. A few rbc and wbc persisted in the urine shortly before discharge. Hg was 11.3 Gm, wbc 6,200 to 9,100. Eosinophilia was 11, 1, and 3 per cent. Urine culture was negative. Total serum protein was 8.0 Gm with 4.1 Gm albumin and 3.9 Gm globulin. The BUN was 13, creatinine 0.87, Ca 11.2, and P 3.9 mg per 100 ml. The serum Na was 142, K 3.3 and 3.2,  $\text{CO}_2$  18, and Cl 100 mEq/L. The lupus erythematosus preparation was negative. Measurement of urinary vanillylmandelic acid was normal as was catecholamine excretion. A phentolamine test was negative. The 24 hour potassium excretion was not increased. The electrophoretic pattern of the serum proteins was normal. The ECG showed left ventricular hypertrophy. X-ray of the chest showed enlargement of the left ventricle. Skull films were normal. Intravenous pyelography showed prompt excretion bilaterally with normal renal architecture. A Howard test was performed and the urine flow and sodium excretion were virtually the same on both sides. A retrograde (femoral) aortogram showed normal renal artery anatomy.

#### *Clinical Course*

During the initial investigation designed to establish an etiological diagnosis, no therapy was given. The diagnostic exclusion of coarctation was made on the physical examination. The tests for pheochromocytoma were negative. Because of the slightly lowered serum K, excretion of K in the urine was measured and found to be normal. There was nothing in the history to suggest pyelonephritis or glomerulonephritis. There was no family history of hypertension, renal or congenital disease. The aortogram failed to reveal renal artery disease. The leading diagnosis appeared to be periarteritis nodosa, because of the transient eosinophilia, isolated left facial weakness, high globulin, appearance of the optic fundi, and the urinary findings. When all the tests outlined above had been completed, reserpine was administered intramuscularly, in a dose of 2.5 mg. The blood pressure fell from 180-190/130-150 to 140/100 mm Hg. With this, it was noted that his speech seemed less slurred and he himself said he felt "less jumpy". Therapy was continued with reserpine 1 mg twice daily by mouth and chlorothiazide 250 mg twice daily. The urines became free of albumin and cells. A renal biopsy was performed yielding a sample containing about forty glomeruli with their associated tubules and blood vessels. "A number of glomeruli reveal small areas of local hypercellularity both at the periphery of the glomerulus and centrally. In some there are adhesions to the capsule. Local mild thickening of the capillary wall is evident, particularly in PAS preparations. With the exception of very patchy arteriolar hyalinization, arterioles and larger vessels appear normal as do tubules. One tubule is plugged by granular blue-grey material which appears to represent focal calcification."

The child has been maintained on reserpine and chlorothiazide and is now (October 1960) well and entirely normotensive.

#### *Comment*

Without a renal biopsy, this child who had a most extensive investigation might have been labeled essential hypertension. This would have been supported by the response to hypotensive therapy. He appears to have some ill-defined intrarenal disorder with glomerulitis and possibly focal tubular disease

or polyarteritis as a cause of his hypertension. Yet antihypertensive therapy has readily controlled his blood pressure and induced clearing of albuminuria and a remission of hypertensive retinopathy.

*CASE 4: Hypertension due to perirenal hematoma (Page Phenomenon)\**

A 4 year old child was well until January 22, 1956 when he developed acute abdominal pain, nausea and vomiting. As the pain became more intense, a physician was called. He observed pallor, and marked tenderness in the right lower quadrant and over the right kidney. The child was promptly admitted to the hospital and by this time the right lower quadrant had become rigid. His hemoglobin was 8.7 Gm and wbc 25,000 with 96% PMN. The urine contained numerous RBC. The blood pressure was 112/80.

*Clinical Course*

An emergency laparotomy revealed a large retroperitoneal hemorrhage arising from the area of the right kidney. About two-thirds of the kidney was visualized and appeared normal. The kidney was therefore not removed.

Immediately postoperatively severe hypertension developed with blood pressure levels ranging from 176/118 to 190/146 with a peak value of 220/190 mm Hg. During the next ten days blood pressure averaged 180/150 mm Hg. Additional episodes of retroperitoneal bleeding were treated by transfusions. Funduscopic examination remained normal. Urines showed 2<sup>+</sup> albumin with red and white blood cells. An intravenous pyelogram revealed good function on the left; on the right, function was poor and the lower pole which was obscured by a mass contained no visible dye at all. On February 10, 1956 a right nephrectomy was performed. As soon as the renal pedicle was clamped, the blood pressure dropped to 110/70, but after removal of the kidney rose again to 120/100 mm Hg. The BUN which had been slightly elevated to 34 mg per 100 ml was normal at time of the nephrectomy. At time of discharge, two weeks postoperatively, his blood pressure was 132/86 mm Hg.

A follow-up examination four and one-half years later revealed blood pressure of 112/70 and negative urinalysis. The resected kidney revealed atherosclerotic aneurysmal dilatation of a branch of the renal artery as the source of intra and perirenal hemorrhage.

*Comment*

The single normal blood pressure recorded before the first exploratory laparotomy might have represented unrecognized shock following the large retroperitoneal hemorrhage. More likely the disturbance in renal hemodynamics was not yet of sufficient magnitude to make the kidney a pressor organ. Nephrectomy was followed promptly by a fall in blood pressure, probably because the very short duration of the hypertension had not yet caused any functional changes in the other kidney. The follow-up period is sufficiently long to say that the patient is cured of his hypertension.

SUMMARY

The importance of measuring the blood pressure during a routine physical examination is as great in children as in adults. This is particularly true since childhood hypertension is virtually always attributable to a specific cause which can be determined by an orderly diagnostic investigation (11). Such investigation must be aimed at all the known etiologies, rare as some of them are.

\* We are indebted to Dr. M. L. Stein and Dr. S. Mishkin for permission to report this case.

If no diagnosis is established by the history, physical examination, laboratory data and urological studies, even angiography and renal biopsy must be performed.

If specific curative therapy, generally surgical, is not applicable, the hypertension should be controlled with antihypertensive drugs, using principles employed in the treatment of adults.

Four cases of hypertension in childhood of unusual interest have been described. One was cured by surgery, two were markedly benefited by a combination of surgery and antihypertensive drugs and one was successfully managed by drugs alone. They illustrate the importance of detailed investigation of every case of childhood hypertension.

Our experience also suggests that home blood pressure readings are of great importance in the successful management of high blood pressure in children.

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# SURGICAL CONSIDERATIONS IN THE TREATMENT OF HYPERTENSION

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The increased availability of effective sympatholytic agents, diuretics and diet has resulted in lessened application of surgical attacks on essential hypertension. A counter-current of interest has, however, developed in the problem of renovascular hypertension, particularly that resulting from occlusive disease of the main renal arteries. This latter interest has in large measure, been stimulated by the increased availability and safety of radiographic techniques for diagnosis and localization, and by a general improvement in the techniques of reconstructive vascular surgery.

It is appropriate at this time to reassess the usefulness and applicability of surgical methods for the treatment of hypertension in relation to both essential hypertension and hypertension of renovascular origin.

## CLASSIFICATION

The number of conditions which can cause an elevation of the arterial blood pressure, either transient or sustained is very large. The following classification is not all inclusive, but is designed as a guide to the surgical approach.

### *I. Secondary Hypertension*

#### A. Renal

##### 1. Congenital:

- a. Cystic disease
- b. Ureteropelvic obstruction
- c. Hydronephrosis

##### 2. Infectious:

- a. Chronic pyelonephritis
- b. Unilateral atrophic kidney

##### 3. Renal tumor (Wilms)

##### 4. Vascular—congenital and acquired occlusive disease of the renal arteries.

#### B. Adrenal:

1. Pheochromocytoma
2. Cushing's syndrome
3. Primary aldosteronism

#### C. Others:

1. Coarctation of the aorta
2. Expanding intracranial lesions
3. Miscellaneous



## II. Essential Hypertension

### ETIOLOGY OF ESSENTIAL HYPERTENSION

There is a historically long and intensive period of laboratory and clinical research regarding the etiology of essential hypertension. Much of this work is elaborated upon elsewhere in this symposium. It does appear probable, however, that this hypertension is initiated and sustained by neurogenic, adrenal, and renal factors, all operating to increase vascular reactivity and heighten arteriolar tone. To this is added the factor of increased intrinsic arteriolar myogenic tone. In fact, a concept of the "vicious circle" has been enunciated, in which any one of these etiologic factors tends to initiate or intensify the activity of the others. For example, unilateral renal hypertension induces hypertensive arteriolar sclerosis in the opposite kidney or neurogenic characteristics. Also, both renal and neurogenic hypertension may produce secondary adrenocortical activity, just as the hypertension of primary adrenal tumors, pheochromocytoma and cortical adenoma may develop renal and neurogenic characteristics. This concept, first enumerated by Volhard in 1931 (1-3) has received much emphasis recently by de Takats (4).

### SYMPATHECTOMY IN ESSENTIAL HYPERTENSION

#### *Case I*

An 18 year old negro female was admitted to the hospital for the ninth time on 6/10/59, complaining of headaches and dizziness of two weeks duration. The patient had a long history, beginning with infantile eczema, and followed by severe asthma and bronchitis which began at the age of eight.

In 1952, at the age of eleven, she was admitted to the hospital with a clinical picture including edema, 4+ albuminuria, hypercholesterolemia, hypoalbuminemia and anemia. Her blood pressure and blood urea nitrogen were normal. A skin and muscle biopsy was normal. The diagnosis of nephrotic syndrome was established and she made a good response to ACTH therapy.

At ages 11½, 12½ and 13½, the patient was readmitted with a classic picture of a nephrotic syndrome. The blood urea nitrogen and the blood pressure were normal. She made a good response to ACTH and bed rest on each occasion although during the intervals between hospitalizations, her urinary sediment showed persistent microscopic hematuria and casts. A diagnosis of chronic glomerulonephritis with recurrent nephrotic syndrome was made and steroid therapy was continued. At age 15 the patient was admitted for evaluation of hypertension. Her blood pressure was recorded at 180/135. She was treated with reserpine and steroids.

In 1957 (age 16) the patient was readmitted because of hypertension (190/120), grade IV hypertensive retinopathy and mild congestive heart failure. Her blood urea nitrogen was 11 mg%. An intravenous pyclogram was normal. A percutaneous kidney biopsy was attempted but was unsuccessful. She was treated with Serpasil, reserpine, mecamlamine and hydralazine, and her blood pressure returned to normal.

In 1958 (age 17) the patient was readmitted with right sided acute otitis externa. The blood pressure was 200/150. Physical examination revealed moderate cardiomegaly and grade I hypertensive retinopathy. The blood urea nitrogen was 11 mg%, albumin 3.3 Gm, globulin 3.4 Gm%; rsp retention was 35% in two hours. The electrocardiogram revealed left ventricular hypertrophy. To her previous antihypertensive regime, chlorothiazide was added. Her blood pressure on discharge was 170/110, and the otitis was treated with antibiotics.

She was admitted in June, 1959, complaining of severe headache of two weeks duration. Physical examination revealed a blood pressure of 190/130, mild cardiomegaly and grade II hypertensive retinopathy. The blood urea nitrogen was 14 mg%, creatinine 1.3 mg%, 24 hour urinary catechol amines 15  $\mu$ g, Na 147 mEq/L, K 4.2 mEq/L,  $\text{CO}_2$  28.1, mEq/L, cholesterol 270 mg% and uric acid 6.8 mg%.

The chest x-ray was interpreted as normal. Electrocardiogram showed mild left ventricular hypertrophy. A lumbar puncture performed on admission indicated a cerebrospinal fluid pressure of 350 mm of water. On biopsy, there was extensive arterioneurosclerosis. Creatinine clearance was 74 cc/min, rsp retention was 60% in two hours. Esbach test indicated 0.3 Gm albumin litre of urine. Digital circulatory studies revealed Work/mg, norepinephrine/min (103 ergs) to be 300; (range for normals is 13-52). On therapy consisting of mecamylamine hydrochlorothiazide, and bed rest, blood pressure returned to 150/90 lying, and 140/104 standing. It was felt that this patient had accelerated essential hypertension.

In July, 1959, the patient had a right sided lumbodorsal sympathectomy and splanchnicectomy. Sympathetic ganglia from D8 to L2, as well as the greater and lesser splanchnic nerves, were resected through an extrapleural, extraperitoneal approach. Postoperatively, there was no change in the blood pressure and her course was uneventful.

In August 1959, a left lumbodorsal sympathectomy from D8 to and including L2 was performed. The greater and lesser splanchnic nerves were also resected. Postoperatively, the patient became normotensive while lying down (BP 140/90). However, she had severe postural hypotension on standing (BP 70/50). After two weeks this disappeared, and the blood pressure lying, sitting and standing remained at 140/100. Her postoperative course was complicated by a large retropleural abscess which was treated by drainage and antibiotics. She was discharged with a blood pressure of 140/100, not taking antihypertensive medication and she maintained this blood pressure for six months after surgery.

#### DISCUSSION

Because of the increasing effectiveness of newly developed hypotensive agents, surgical attacks on essential hypertension have been almost completely abandoned. There is, however, a place for surgical procedures when medical therapy has failed, particularly in young patients with an accelerated form of the disease (5).

The most widely used surgical approach has been some form of sympathectomy. Several different techniques have been advocated, each devised to interrupt partially the pathways between the nerve centers and the fibres going directly to the blood vessels. It has been postulated that this procedure will produce a reduction in arteriolar spasm, and an increase in blood supply to the kidney and adrenal glands. Several approaches have been recommended: 1) subdiaphragmatic resection of the splanchnic nerves, a portion of the coeliac ganglion, and the upper lumbar trunks to include the upper two lumbar ganglia. Adson, (6) who first carried out this procedure in 1936, believed that this procedure denervated the adrenals and the splanchnic and renal arteriolar beds. 2) Suprardiaphragmatic resection of the 11th and 12th dorsal ganglia, and the greater, lesser and least splanchnic nerves bilaterally was first performed by Peet (7) in 1933. 3) Bilateral thoracolumbar resection including the sympathetic chain from the 8th dorsal to the 2nd lumbar ganglia, with resection of the greater, lesser and least splanchnic nerves, as advocated by Smithwick, has received the widest surgical application (8).

On anatomical grounds, Mitchell has suggested that the removal of the sym-

pathetic chains from D4 to L3, along with all the splanchnic nerves, would give the best denervation of the adrenal, splanchnic and renal arterioles. It would also denervate the vessels of the lower limb. Such a procedure has been carried out by Hinton, Poppin and others (9, 10).

Another procedure which has received considerable attention in the management of essential hypertension is adrenalectomy, either total or subtotal (11). While there is no evidence that the adrenal glands initiate essential hypertension, there is much to suggest that they play a significant role in the maintenance of the elevated blood pressure. Such evidence includes the fact that Addison's disease is associated with hypotension, and the work of Deone (12), describing increased size of the zona glomerulosa and increased renin production in experi-

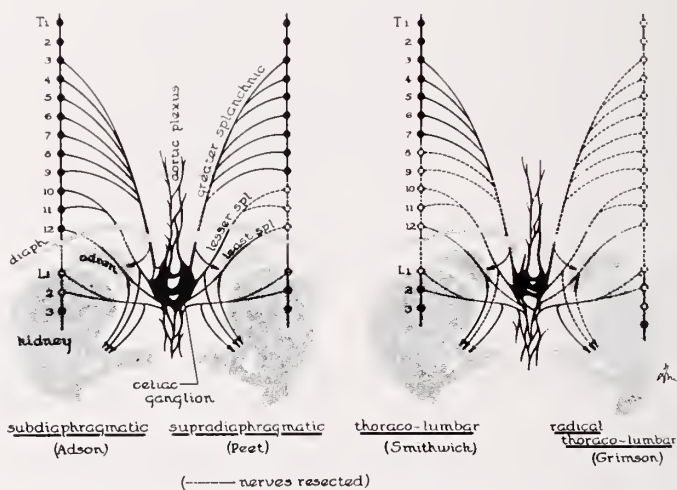


FIG. 1. The types of sympathectomy available in the treatment of essential hypertension are shown.

mental perinephritis. Goldblatt discovered that hypertension induced by clamping one renal artery could be abolished by adrenalectomy (13). Increased size of the adrenal glands in human hypertension has also been reported (14, 16).

A great difficulty in assessing the role and value of either sympathectomy or adrenalectomy in the treatment of essential hypertension, is the fact that no uniform classification of the severity of the disease has been applied. In a review of 2,708 cases of sympathectomy, Smithwick concludes that the procedure offers several benefits (5). In patients followed for 10 to 19 years, 50 per cent showed a reduction in blood pressure, 34 per cent were unchanged and 16 per cent were worse. In assessing evidence of cardiovascular disease in the same patients followed for the same length of time, 42 per cent were improved, 21 per cent unchanged and 37 per cent worse. With regard to symptoms, 70 per cent were improved, 5 per cent were unchanged and 25 per cent were made worse. The problem of assessing the effect of surgical treatment on mortality from essential hypertension is even more complex. It may, however, be said that sympathectomy

has significantly increased long range survival of patients with essential hypertension (5).

A recent interesting comparison of 114 patients having thoracolumbar sympathectomy with 116 patients having subtotal or total adrenalectomy and a limited Adson type of sympathectomy revealed during a 3 to 7 year follow-up period that: a) The operative mortality following sympathectomy was less than one per cent and following adrenalectomy 5 per cent. Seventy-three per cent of the sympathectomized and 68 per cent of the adrenalectomized patients survived the follow-up period. b) The authors believed that results in terms of blood pressure levels, ECG, heart size and ocular fundal changes were clearly superior for the adrenalectomy group. c) Angina and congestive failure appeared to be markedly alleviated by adrenalectomy (17).

While it is certainly true that surgery for essential hypertension has been largely replaced by effective medical control, either sympathectomy or adrenalectomy is of value to those who are unresponsive to medical therapy, or who will not follow it, or in young hypertensive subjects where the disease progresses rapidly. Where congestive heart failure is a dominant feature, adrenalectomy may be the better procedure (17).

#### SURGICAL MANAGEMENT OF RENOVASCULAR HYPERTENSION

While it is true that renovascular hypertension constitutes a minority of the cases of hypertension seen clinically, a marked interest in this condition is being evoked because application of reconstructive vascular techniques now available may both conserve renal function and cure the hypertension.

#### *Representative case*

##### *Case II*

A 38 year old Puerto Rican female was admitted to the hospital because of headache and parasthesia.

In 1954, during her second pregnancy, this patient was admitted for the first time with a blood pressure of 165/115. This was unassociated with edema or albuminuria. At this time, the eye grounds showed grade I hypertensive retinopathy, but the heart was normal in size and the ECG was normal. Her blood urea nitrogen was 18 mg%, uric acid 10.6 mg%, and urinalysis negative. She was delivered of a stillbirth in the 34th week of gestation.

In October, 1955, she again delivered a stillbirth. At this time, her blood pressure was 200/130. She was treated with bed rest, reserpine and acetazolamide. A diagnosis of thyrotoxicosis was made on the basis of clinical signs and a serum protein-bound iodine of 8.9. This was treated with methimazole. She was discharged improved with a blood pressure of 140/100. In 1957 a therapeutic abortion and tube ligation were performed in Puerto Rico.

In October 1959, the patient was again admitted to the hospital with headache and transient numbness of the left side of the face and left arm. Physical examination revealed a blood pressure of 210/130 and severe retinopathy with papilloedema, hemorrhages and exudates. There was no cardiomegaly. Spinal fluid pressure was 300 mm of water.

Diagnostic studies indicated a Hg of 12.2 Gm, wbc 15,200, esr 2 mm/hour. Urinalysis was negative. Blood urea nitrogen was 18 mg%, and creatinine 1.1 mg%. The timed intravenous pyelogram and Howard test were normal. However, the right kidney was seen to be 2.0 cm smaller than the left. The phenotamine test was negative. An orthograde aortogram per-



formed by rapid injection of dye into the venous system showed a narrowing of the origin of the right main renal artery, and a small accessory right renal artery.

The patient's hypertensive encephalopathy was treated with intramuscular reserpine, with a prompt reduction of blood pressure to 160/100 and abatement of neurologic symptoms

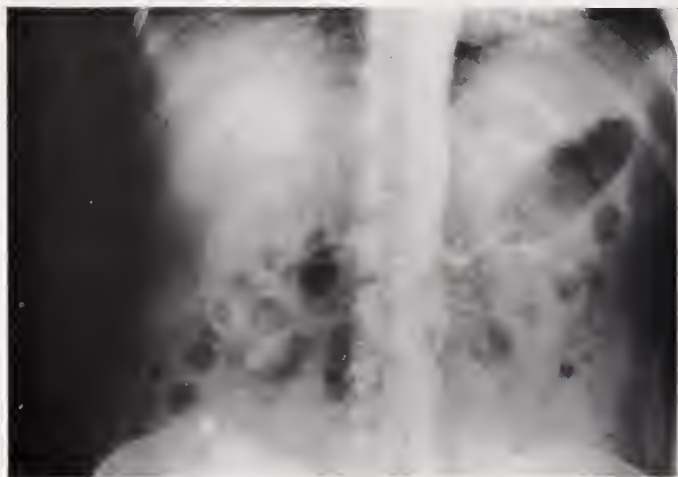


FIG. 2. Case II—A venous aortogram before surgery. The right kidney is smaller, and has two renal arteries, one of which has a stenotic area at its origin.



FIG. 3. Case II—A postoperative venous aortogram. The iliac-renal artery shunt is patent.

In January, 1960, the right kidney was explored. It was supplied by a small superior artery and a moderate-sized inferior renal artery, both coming directly from the aorta. The inferior renal artery had a palpable short area of narrowing at its point of origin from the aorta, with a palpable systolic thrill beyond the obstruction. A crimped Dacron arterial graft was inserted from the right common iliac artery to the right inferior renal artery at a point just distal to the obstruction. The anastomosis was end of graft to side of vessel on each side.

The patient's postoperative course was uncomplicated. Immediately postoperatively, the

blood pressure was 120/90. However, two weeks postoperatively, the blood pressure had risen to 140/103. At the time of discharge, the patient had a protein bound iodine of 6.4, blood urea nitrogen of 12 mg, a negative urinalysis and rsp excretion of 25 per cent in 15 minutes. In January, 1960 the patient's blood pressure was 170/120 and in April of that year it was 150/110.

Three months after operation, the blood pressure was 170/120, and therapy was started with synosinopine, mecamlamine and other drugs. She was readmitted for evaluation in May, 1960. At this time her blood pressure was 150/100. The physical examination was normal except for slight arterial narrowing in the fundi, and a well healed abdominal scar.

The hg was 12.2 Gm, wbc 15,000, urinalysis negative. Blood sugar levels, serum Ca, K, P, cholesterol and creatinine were normal. Blood urea nitrogen was 18 mg%. The chest x-ray and electrocardiogram were normal. The intravenous pyelogram showed prompt visualization bilaterally after three minutes. A venous aortogram showed the right kidney to be smaller and more poorly opacified than the left. The shunt from the right common iliac to the right renal artery was patent. The patient was on a low salt diet and was given *Rauwolfia* crude root. She was discharged with a blood pressure of 140/90. One year after operation, the patient was asymptomatic and her blood pressure 170/110, despite treatment with chlorothiazide and reserpine.

#### DISCUSSION

Occlusive lesions of the renal arteries or their major branches are now recognized as the most common remediable cause of renal hypertension (18). Although Bright (19) first recognized this association more than one hundred years ago, and renal hypertension has been the object of intensive laboratory and clinical study, the physiologic mechanism by which renal arterial disease and hypertension are associated has resisted elucidation. Carrel and Janeway in 1909 reported an elevation of blood pressure following a reduction in renal blood flow (20, 21). However, the classic experiments of Goldblatt published in 1934 initiated intensive studies on the origin of renovascular hypertension. So much has been written on the Goldblatt (22) type of "renal ischemic hypertension" that it is of little value to reiterate it here. However, it should be stated that current investigations (23, 24) tend to show that hypertension of renal vascular origin, whether clinical or experimental, is probably caused by an alteration in the pulse pressure wave reaching the kidney, to which it is believed to respond by the release of renin. The renin is acted upon to form a decapeptide. The decapeptide, acted upon by a converting enzyme in the blood which splits off hystadyl leucine, is converted to a highly pressor octopeptide, angiotensin.

The occlusion of the renal artery is usually produced by an arteriosclerotic plaque located at the orifice of the vessel. In a smaller number of cases there may be a stenosis due to subintimal fibrosis or fibromuscular subintimal proliferation. Renal artery thrombosis or dissecting aneurysm of the renal artery may also cause occlusion. The kidney beyond the obstruction may appear normal, or may show evidence of tubular atrophy or frank segmental infarction.

The prime requisite for the diagnosis of this form of hypertension is a high index of suspicion, particularly in cases of hypertension which a) appear in a patient under 35, b) develop or worsen following an attack of flank pain, c) occur over the age of 55 in the malignant form, or d) are of recent origin and progress rapidly. This condition should also be suspected e) when there is disparity in the

size of the kidneys on flat film or f) where there is a disparity in function on pyelography.

Considerable attention has been given to the use of differential renal function studies in establishing the diagnosis, including comparative renal excretory pyelography, the Howard test (25) which consists of measuring the water and sodium output of each kidney, and bilateral percutaneous renal biopsy. Estimation of renal plasma flow by the measurement of para-aminohippuric acid clearance, and of glomerular filtration by measurement of inulin clearance has also been used. Considerable recent attention has been given to renography by the intravenous injection of radioactive iodopyracet with bilateral flank screening.

Notwithstanding the usefulness of these tests, they remain primarily confirmatory. The essential and definitive study in the diagnosis of hypertension resulting from occlusion of the renal artery is the renal arteriogram. While relatively good results are usually obtained by the Steinberg technique of orthograde arteriography by the venous route, the most consistent results are obtained by percutaneous translumbar aortography. Cooley has reported on 1,200 such examinations without mortality or significant complication (18).

The therapeutic approach to hypertension of renovascular origin is surgical. The alternatives may be classified as follows:

1. Excisional—a. Nephrectomy  
b. Partial nephrectomy or excision of infarcted area
2. Angioplasty—a. "Patch" graft over a stenotic area  
b. Endarterectomy  
c. Resection of the stenotic area and end-to-end anastomosis
3. Arterial by-pass—a. Synthetic graft  
b. Splenorenal arterial anastomosis

The choice of procedure depends on the nature of the lesion (18, 27). Where marked and obvious renal atrophy is present, nephrectomy is the procedure of choice. If the lesion is a highly localized one, endarterectomy or excision with end-to-end anastomosis can be performed. In certain stenoses, the area can be widened by the placement of a diamond-shaped patch graft into the wall of the vessel to allow localized widening of the lumen.

Most recent interest has been centered on aorticorenal by-pass by means of synthetic grafts. The material chosen is usually crimped Dacron.

Poutase and Dustan, in a recent review, reported on 71 patients with hypertension due to renal artery lesions (28). Of these, 47 were submitted to surgery; five died within two months of operation. Of the remaining 42, diastolic hypertension disappeared in 32; in four, blood pressure was somewhat reduced, and in six it was unchanged.

Morris and his co-workers, in a recent report of more than 75 patients with renal hypertension treated surgically, stated that 82 per cent had a restoration of normal blood pressure (29). They also stated that of their cases, 35 per cent had bilateral disease.

While this field of vascular reconstruction is too new for final assessment, the results reported by these investigators emphasize the importance of the diagnosis of surgically remediable renal hypertension.

## SUMMARY

A. Two cases of hypertension treated surgically are reported.

B. The medical treatment of essential hypertension has sharply limited the applicability of sympathectomy.

C. The pathology and management of hypertension of renovascular origin is described. Emphasis is placed on early diagnosis of this condition, and on the angioplastic and by-pass techniques available for treatment of the renovascular obstruction.

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# MANAGEMENT OF HYPERTENSION IN THE PREGNANT WOMAN

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## I. INTRODUCTION

About five per cent of all pregnant women have elevation of blood pressure, thereby making this one of the leading complications of pregnancy today. It has been estimated that a woman has a thirteen per cent chance of developing hypertension at least once in her childbearing career. (1) Furthermore, the Office of Vital Statistics lists toxemia of pregnancy as the prime cause of maternal mortality in the continental United States. The newborn is not spared either, since toxemia is a major reason for stillbirth. In addition, toxemia has been statistically correlated with subsequently appearing neuromuscular disturbances in children (2). The cause of toxemia of pregnancy is unknown. Toxemia is found only in the pregnant human female.

Careful consideration of each patient individually is imperative. An occasional patient may have a reversible form of hypertension masquerading as toxemia, or a pheochromocytoma with a fifty per cent mortality rate in pregnancy (3). Studies of pregnant women disclose that essential hypertension, contrary to former opinion, may be clinically diagnosed in young women. The relation of toxemia of pregnancy to subsequent essential hypertension may give clues to the etiology of the latter. Exact diagnosis has important prognostic significance in perinatal salvage.

## DIAGNOSIS

The blood pressure level constituting hypertension is usually given as 140/90. Some authorities believe 130/80 would be a more realistic level for the pregnant woman (see Functional Changes). To avoid the effects of apprehension, a nurse should record the blood pressure with the patient at rest. A very heavy arm (circumference over 47 cm) should have 15 mm subtracted from the blood pressure readings. Average blood pressure recordings tend to increase with age (4). In labor (especially the late first stage or second stage) blood pressure rises 10 to 20 mm in most pregnant women.

It is estimated that five per cent of all pregnant women have hypertension. Various reports range from two to twelve per cent. In former years, any pregnant woman with elevated blood pressure was considered to have "toxemia". Aside from this "catch-all" diagnosis, variable criteria, variable percentages of home-hospital deliveries, and variable antepartum observation have made such data quite vulnerable. Unfortunately, for ease of retrospective study, the labels "preeclampsia" or "toxemia" are currently used in some areas for a diastolic blood pressure of 90 mm or over on two occasions during any part of the

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pregnancy (5). There are many possible causes of hypertension in the pregnant woman. The first step in management is proper diagnosis. The term "toxemia" has been variously and loosely applied to pregnant women with preeclampsia, eclampsia, and any disease causing hypertension or coma. "Toxemia" should be reserved to describe only preeclampsia or superimposed preeclampsia and the eclampsia which may follow from it. It is wise to avoid or carefully define the term "toxemia" or use a more specific label.

Most (58.6%) pregnant women with hypertension have preeclampsia (6). Synonyms include "specific hypertension of pregnancy" and "acute toxemia". In the United States the standard classification (although arbitrary) is that of the American Committee on Maternal Welfare (7).

*I. Acute Toxemia of Pregnancy (onset after the twenty-fourth week)*

A. Preeclampsia

1. Mild
2. Severe

B. Eclampsia (convulsions or coma, usually both, when associated with hypertension, proteinuria, or edema)

*II. Chronic Hypertensive (Vascular) Disease with Pregnancy*

A. Without superimposed acute toxemia (no exacerbation of hypertension or development of proteinuria)

1. Hypertension known to have antedated pregnancy.
2. Hypertension discovered in pregnancy (before twenty-fourth week and with postpartum persistence.)

B. With superimposed acute toxemia.

*III. Unclassified Toxemia (Data insufficient to differentiate the diagnosis)*

The criteria for the diagnosis of preeclampsia are the development after the twenty-fourth week of pregnancy of one or more of the following:

(1) Systolic blood pressure of 140 mm Hg or more, or a rise of 30 mm or more above the usual level.

(2) Diastolic pressure of 90 mm or more, or a rise of 20 mm above the usual level.

(3) Proteinuria of a significant degree.

(4) Persistent edema. Abnormal blood pressures must be noted on at least two separate occasions at least six hours apart. Proteinuria must be observed in clean or catheterized urines on two or more successive days. Preeclampsia is classified as severe if any one of the following is present:

(a) systolic blood pressure of 160 mm or more, or diastolic of 110 mm or more on two separate occasions with the patient at rest.

(b) proteinuria of 5 Gm or more in 24 hours.

(c) oliguria of 400 cc or less per 24 hours.

(d) cerebral or visual disturbances.

(e) pulmonary edema or cyanosis.

Unfortunately the classification implies a mild and severe form of pre-

eclampsia and lulls one into a false sense of security. The truth is that preeclampsia is a treacherous disease and can be rapidly progressive. Furthermore pathological and physiological studies reveal that preeclampsia and eclampsia are part of the same disease process and that death can occur without a convulsion. Each case should be carefully managed regardless of apparent severity or of apparent classification.

Clinically preeclampsia is a disease process with an insidious, progressively worsening sequence of events whose pace may accelerate suddenly. Symptoms usually develop late in the course of the disease. However, retrospective studies suggest that before some patients develop preeclampsia they may have only vague symptoms. The first sign of preeclampsia is weight gain of over one pound per week due to fluid retention which may start as early as the twentieth week of gestation. Characteristically, preeclampsia is a disease of the third trimester when the rate of weight gain accelerates with the appearance of foot and ankle edema (tight shoes), periorbital edema (often with an infraorbital white line), digital swelling (difficulty in removing rings), and pretibial fluid collection. Hypertension follows. Although the preeclamptic patient may be quite ill and go on to develop eclampsia, the blood pressure usually does not go beyond a modest elevation of systolic 130 to 160 mm and diastolic 80 to 110 mm. Blood pressure levels of over 160/110 imply another factor such as pre-existing essential hypertension. Furthermore, the blood pressure readings in preeclampsia do not vary greatly when recorded every hour or two. With elevation of blood pressure the optic fundi may disclose segmental or generalized arteriolar spasm. "Retinal sheen" due to edema has not always been reliable as a diagnostic criterion. Presumably in otherwise uncomplicated preeclampsia the retina will not have old damage of chronic hypertensive or renal disease. Proteinuria develops after hypertension. The amount of proteinuria can change very suddenly. Finally, definite symptoms appear with frontal headaches, vertigo, tinnitus, visual disturbances, drowsiness, nausea, vomiting, epigastric distress, apprehension and excitability. Examination now may reveal hyperreflexia and ankle clonus. Oliguria supervenes. A sense of thoracic pressure or epigastric pain or further hyperreflexia may herald the onset of generalized tonic and clonic convulsions. This terrifying occurrence commences with a peculiar stare of the eyes in the puffy face and perioral and facial twitches. The entire body becomes rigid and the arms flex. Suddenly starting with the jaw and spreading to the rest of the body there are violent convulsions. The reddened eyes bulge, the face is purple, and bloody foam leaks from the mouth. There is no breathing during the convulsion. After a few minutes the convulsions finally stop, the patient lapses into coma, and starts to breathe again with some difficulty. Later the patient is found not to have any recollection of the convulsive episode. If the patient was unattended she may have injured herself by thrashing about or biting the tongue. Among eclamptics, the convulsions occur before labor in fifty per cent of cases, intrapartum in 25 per cent and within 24 hours of delivery in the remaining 25 per cent. Severe proteinuria and oliguria are common. Poor prognostic signs are: an increasing number of convulsions, prolonged time



lapse between the first convulsion and delivery, persistence of coma, high fever, pulse rate of over 120 per minute, cyanosis and hemoglobinuria. Fatal outcome which occurs in five per cent of cases, may be associated with pulmonary edema, cardiac failure, acute hypotension, coma, massive cerebral hemorrhage, and pneumonitis. In patients who recover, there is a five per cent chance of puerperal psychosis which may persist for a month postpartum, and possible transient blindness as a result of retinal detachment. Fortunately over the past forty years there has been a general worldwide reduction in fatality following eclampsia. It has been suggested that this has occurred because of less iatrogenic disease produced by misguided therapy, better obstetrical training and improved prenatal health. The real cause, however, remains unknown.

The uterus in preeclampsia is thought to be irritable and statistically there is a tendency towards premature labor. Delivery occurs in most women with eclampsia within 24 hours partly because of induction of labor and partly because of spontaneous onset of labor.

The symptoms of "pure" preeclampsia subside in anywhere from several days to several weeks after evacuation of the uterus and then the patient should appear normal. Eclamptic convulsions may occur up to 24 to 48 hours after delivery. Any convulsion after that time should be viewed with suspicion. Convulsions or coma may occur in pregnancy from conditions other than eclampsia, for example: epilepsy, hypertensive encephalopathy, uremia, hysteria, hyperventilation, alkalosis, insulin overdosage, diabetic coma, central nervous system pathology (tumor, abscess, trauma, thrombosis, meningitis), chorea gravidarum, shock, local or general anesthetic poisoning and sickle cell (hemoglobin C) disease.

Death of the fetus with its retention in the uterus often does not cure pre-eclampsia. An interesting speculation is raised by demonstrating that placental circulation either may be intact or closed after fetal death (8).

Infrequently preeclampsia apparently commences several days or up to two weeks after delivery. This may represent up to five per cent of all cases of preeclampsia. In such a situation it is important to rule out other illnesses. Nevertheless, it may be true preeclampsia. It is usually mild and often lasts but a few days. Perhaps certain of these patients were actually preeclamptics before delivery, whose signs were masked by routine low salt diet and liberal use of diuretics. In the postpartum period because of discontinued therapy the signs of preeclampsia would return to what they would have been otherwise.

Rarely two or three weeks after an apparently normal pregnancy there may be acute renal failure from sudden rapid progression of a previously unrecognized chronic glomerular nephritis or chronic interstitial nephritis (9).

Certain women have a predisposition to preeclampsia-eclampsia (10). The primigravida is the prime target, particularly the very young and also those over thirty years of age. The incidence of preeclampsia in twin gestation is 19 per cent, and in the primigravida with twins about 25 per cent. Multiple gestation poses the additional problems of anemia and premature labor. The disease is more frequent in clinic patients than in private patients. In the United States it is more frequent in the negress than in the white woman. Certain pre-existing

illnesses predispose to preeclampsia, particularly essential hypertension, and possibly diabetes mellitus, chronic renal disease, obesity and migraine headaches. It has been suggested that patients with emotional conflicts arising from pregnancy, personality defects and guilt feelings also are susceptible. The disease is found in 35 per cent of patients with hydatidiform mole, a massive grape-like cluster of swollen placental villi practically always without any sign of a fetus. This may cause preeclampsia early in pregnancy. With a mole, the uterus enlarges faster than would be expected. The chorionic gonadotropin titer of blood or urine is markedly elevated. Whereas in a normal pregnancy at sixteen weeks gestation there are fetal movements felt, a fetal heart beat heard, and a fetal skeleton seen on x-ray, none of these obtain in a mole. Preeclampsia often develops when the uterus reaches the height of the umbilicus. Usually the mole makes itself known by repeated episodes of vaginal bleeding and finally the passage of tissue. Definitive treatment of the mole and the preeclampsia is evacuation of the uterus. The possibilities of hemorrhage and malignant transformation must always be kept in mind.

The etiology of preeclampsia is unknown. Any hypothesis should account for the occurrence of the disease only in the human female during pregnancy, or the immediate puerperium and the predisposition of certain patients to the disease. Based on the therapeutic response to uterine evacuation and antihypertensive drugs a hormonal rather than a neurogenic mechanism is suggested. It is not known whether the decreased uteroplacental blood flow is a causative factor or a result. Some of the more popular hypotheses are listed with their protagonists, but none has been generally accepted (10).

1. S. J. Browne: The normal placenta inactivates excessive corticosteroids and thereby avoids a Cushingoid Syndrome (preeclampsia). Protective placental activity decreases with reduction of oxygen tension from uterine ischemia.

2. E. W. Page: The ischemic placenta releases into the maternal blood a substance which produces toxemia in susceptible subjects. Susceptibility may be the result of sodium retention.

3. J. L. Mastboon: Placental ischemia results in failure of mineralo-corticosteroids formed in the placenta to be converted by the placenta into progesterone-like substances.

4. R. A. Bartholomew: Placental infarcts release a toxin into maternal blood.

5. J. Sophian: Uterine resistance to the stretching effect of pregnancy causes a "uterorenal reflex" with decreased effective renal blood flow by an arteriovenous shunt.

6. B. Wylic: Toxemia is an evolutionary postural disease, unknown in quadrupeds, and caused by the uterus compressing the upper urinary tract structures.

7. Sensitivity reactions have been proposed to placental polysaccharides, placental globulin, and as a generalized Schwartzman phenomenon to thromboplastin.

8. G. C. Lennon and Gardiner, J.: Noradrenalin metabolism defect.

a.) Mendlowitz, M., Altehek, A., and Naftchi, N.: Inadequate supply of O-methyl transferase to degrade noradrenalin (11).

9. Theobald, G. W.: Dietary deficiency and mechanical factors.
10. Hunter, C. A. Jr., and Howard, W. F.: A pressor substance, hysteroxin, elaborated in utero and found in amniotic fluid (12).

#### DIFFERENTIAL DIAGNOSIS

The disease most frequently confused with preeclampsia is essential hypertension. Typically there is hypertension before, during and after pregnancy. The patient is often an older, multiparous woman with a history in prior pregnancies of "recurrent toxemia" and a family history of high blood pressure. There is no edema or proteinuria in otherwise uncomplicated essential hypertension in pregnancy. In mild or early cases there is no organ involvement such as cardiac enlargement, renal impairment, retinopathy, or cerebro-vascular lesions. In addition in mild cases in midtrimester of pregnancy there may be a temporary reduction of blood pressure to "normal" limits of less than 140/90. If such a patient were first seen in midtrimester and found to be normotensive and then had a rise of pressure in the last trimester, she might pose a diagnostic problem. Either the rising pressure is essential hypertension returning to its usual level or it is preeclampsia. Laboratory tests, to date, even a battery of five (12), can not differentiate the two conditions in the individual patient. The diagnosis rests on clinical judgment. The main clues are a lack of excess weight gain, a lack of edema and a lack of proteinuria in the patient with essential hypertension. Such a patient may be obese or thin but she is not puffy with fluid retention. Furthermore the blood pressure may be labile and vary markedly with physical activity, apprehension, or rest. With severe, fixed, or long standing essential hypertension the blood pressure may not dip in midtrimester and may be in a high range of systolic 170 to 210 mm and diastolic of 100 to 120 mm. In contradistinction in preeclampsia the hypertension is in a lower, middle range and even in severe cases may only be 160/100. Also in preeclampsia there is little tendency for the pressure to vary during short time intervals. In recent years with more frequent observations of patients, there has been a trend throughout the United States to diagnose preeclampsia less often and to diagnose essential hypertension more often. Some authorities even go so far as to automatically diagnose essential hypertension rather than preeclampsia simply because the patient is multiparous or over thirty years of age. There has been found a group of pregnant women who have been diagnosed as having essential hypertension even though they may be young primigravidas. Their disease is early and labile and they may be normotensive after pregnancy. This observation invalidates age alone as a criterion for essential hypertension. Either more frequent examinations in pregnancy cause us to discover essential hypertension in young women, or pregnancy itself brings out latent essential hypertension.

The pregnant woman with essential hypertension has anywhere from a 15 to 30 per cent chance of developing superimposed preeclampsia. The probability of superimposition is not always dependent on severity of the essential hypertension. There is an accumulation of edema fluid, followed closely by exacerba-

tion of blood pressure (minimum systolic increase of 30 mm and diastolic increase of 15 mm) and proteinuria. Such patients have the most serious fetal and maternal prognoses. They may go on to eclampsia or may develop various complications. The nature of the superimposition of preeclampsia on essential hypertension has been debated in the past. Dieckmann believed that it represented a worsening of the basic disease process (in other words worsening of the essential hypertension). Renal biopsies with electron microscopy disclose that superimposition of preeclampsia is truly the addition of the separate disease preeclampsia and not worsening of the original disease process (14).

Unfortunately there is a "special threat" type of patient in this group who:

- (1) is multiparous and does not bother to go for the prenatal care.
- (2) is anemic.
- (3) is over 35 with a vascular system which can not cope with sudden changes.
- (4) has essential hypertension with organ involvement.
- (5) develops superimposed preeclampsia.

(6) finally seeks medical care after an additional complication such as premature separation of the placenta, acute anuria, etc. develops. Such "special threat" patients are replacing young primigravida eclamptics in mortality lists. Young primigravidas often seek medical care early and have resilient vascular systems. Furthermore eclampsia itself is preventable.

Concerning incidence of various causes of hypertension in the New York area, about 60 per cent have preeclampsia, 1.4 per cent have eclampsia, 28 per cent have essential hypertension, and 9 per cent have essential hypertension with superimposed preeclampsia.

The next largest group of diseases to be differentiated from preeclampsia are the renal diseases. Foremost among these is pyelonephritis. The acute case is easily diagnosed by a shaking chill, high fever, lumbar pain, proteinuria, pyuria and positive urine culture. There is no weight gain, edema, hypertension or retinal change. At autopsy pyelonephritis, is found to be one of the leading causes of chronic renal disease (15). Paradoxically, pyelonephritis is relatively infrequently diagnosed in the living patient. It would seem that the disease can be present and progress without the usual symptoms or signs. The clinical state of incipient renal failure (abnormal renal function tests, inability to concentrate urine, urea retention, and hypertension) may be similar in almost all chronic renal diseases regardless of etiology. Pregnancy (with its hydronephrosis and urinary stasis) compromises the kidney, makes it susceptible to infection from bacteria even of otherwise low pathogenicity, and also favors ascending infection. Resolution of pyelonephritis may be incomplete, leaving smoldering interstitial pyelonephritis and focal scarification which may defy diagnosis, and which may make the kidney more susceptible to further attacks. Whereas scars of prior pyelonephritis would appear to invite recurrences in pregnancy, it is uncertain whether other pre-existing renal diseases also increase vulnerability to both obvious and silent pyelonephritis. Renal damage in pyelonephritis is caused by bacterial infection (hematogenous, and colon lymphatic as well



as intraluminal ascending infection) and possibly by "auto-immune" hypersensitivity mechanisms.

Some thoughts as to practical management are:

- (1) keep catheterization and manipulation of the bladder to a minimum and use meticulous care.
- (2) encourage fluids to avoid a small urinary flow of less than 1000 cc daily.
- (3) avoid excessive spice or coffee in the diet which might cause dysuria and confuse the problem.
- (4) consider the diagnosis of pyelonephritis in any renal disease as a primary or secondary factor.
- (5) be wary of situations causing bacteremia.
- (6) instruct the patient in perineal hygiene.
- (7) do frequent urine analyses of clean voided specimens, together with cultures and bacterial colony counts, especially in suspect cases.
- (8) rule out specific urological causes of recurrent infections such as stricture and calculus. Obvious acute pyelonephritis is vigorously treated with appropriate antibiotics in accord with sensitivity tests. Treatment should be continued for about five days after apparent cure. Before the culture is reported, a relatively safe drug to use is Sulfisoxazol 2 Gm as an immediate oral dose and thereafter 1 to 2 Gm every six hours. Fluids are encouraged.

The most important question to be raised is the prophylactic use of medication during pregnancy to prevent pyelonephritis if the patient has had:

- (1) obvious acute pyelonephritis recently or in the previous or current pregnancy, or
- (2) if the patient has chronic renal disease. Antibiotic prophylaxis is really effective only for very sensitive organisms that never become resistant, and these are not the culprits. Unfortunately antibiotic prophylaxis does not seem to be effective in preventing pyelonephritis. If prophylaxis is nevertheless to be attempted, probably it should be planned for the last trimester, with intermittent doses and employing methenamine mandelate and/or the sulfonamides. The more potent antibiotics should be reserved for obvious clinical infections.

Chronic glomerulonephritis may mimic preeclampsia. It is suggested by proteinuria and casts present before the 20th week of gestation. There may be a history of previous episodes of renal disease and hypertension and retinal vascular changes may be present. Occasionally a nephrotic phase develops with proteinuria, edema, hypoproteinemia, doubly-refractile bodies in the urine, hypercholesterolemia, and with normal blood pressure. The diagnosis of subacute glomerulonephritis was made by renal biopsy on one of our patients whose clinical picture resembled preeclampsia. Without this biopsy, it could be incorrectly inferred that the patient's continued illness after delivery represented severe preeclampsia causing chronic renal-hypertensive disease. Acute glomerulonephritis is very rare in pregnancy. It closely resembles acute preeclampsia. In addition to severe proteinuria, oliguria, and hypertension, there may be a history of antecedent streptococcal infection, gross or microscopic hematuria, and resistant edema.

The first indication of the presence of congenital polycystic kidneys may be an

acute pyelonephritis. Sometimes bilateral, irregular enlarged kidneys may be palpated. Proteinuria and hypertension may be present in later stages. There are many patients with this disease who remain asymptomatic and undiagnosed during repeated gestations as long as renal function is adequate and there is no infection.

Lupus erythematosus with renal involvement may resemble preeclampsia (16). There may be central nervous system manifestations, arthritis, chronic skin disease, and a false positive serology.

Possible "curable" unilateral renal disease may be caused by renal artery obstruction, renal infarction, or old chronic unilateral pyelonephritis.

Coarctation of the aorta may cause any degree of hypertension in pregnancy, including intermittent hypertension with a sustained blood pressure rise late in pregnancy (17). Diagnostic suspicion should be aroused by: a basal systolic murmur heard well over the upper back, an aortic diastolic murmur present in one-third of cases, absent or reduced pulses in the lower extremities, prominent vascular pulsations in the neck and vascular rib notching on x-ray.

Systolic hypertension produced by increased cardiac stroke output may be seen in thyrotoxicosis, aortic insufficiency and heart block. Arteriosclerosis of large vessels may also cause systolic hypertension.

Pheochromocytoma, although rarely found with pregnancy, is reputed to have a fifty per cent maternal mortality rate (3). There may be episodes of headache, nervousness, sweating, palpitation and intermittent or continuous hypertension. Some clues are a palpable mass, von Recklinghausen's neurofibromatosis, glycosuria and hyperglycemia. Intravenous pyelography may sometimes demonstrate a kidney displaced by the tumor. The provocative histamine test and pressure reducing phentolamine test are potentially dangerous because of violent pressure changes. A maternal mortality has been caused by the latter, as well as fetal deaths (18). The safest diagnostic methods are demonstration of elevation of urinary catecholamines and especially, elevation of urinary vanillylmandelic acid (19). If a pheochromocytoma is suspected, then diagnostic elimination or corroboration is imperative. Surgical removal of the lesion during pregnancy is recommended.

Cushing's syndrome may cause hypertension, but the diagnosis is suggested by obesity of the face, neck and trunk, hypertrichosis, purplish abdominal striae, polycythemia, hyperglycemia, glycosuria, hyperkalemic alkalosis, osteoporosis and increased urinary 17-hydroxy-steroid excretion. Pregnancy in such patients is unusual. Hypertension caused by primary hyperaldosteronism is rarer and may be associated with intermittent episodes of weakness, polyuria, polydipsia, a neutral or alkaline urine of low specific gravity and a low serum potassium.

Hypertension may be produced by bulbar poliomyelitis, and increased intracranial pressure as in turn caused by brain tumor, subdural hematoma, and subarachnoid hemorrhage. The latter may give a picture closely resembling sudden severe preeclampsia-eclampsia. Blood in a spinal fluid tap is diagnostic. Renal biopsy is an auxiliary tool to rule out preeclampsia-eclampsia.

Acute exacerbations of porphyria may produce hypertension with retinal

arteriolar spasm and temporary blindness. Labor and drugs can worsen the disease. Phenobarbital may be potentially lethal. Some symptoms are severe abdominal pain, psychoses, nerve palsies and central nervous system disturbances. Diagnosis is made by examination of the urine for porphobilinogen (20). Approximately twelve cases of this disease in association with pregnancy have been reported.

A maternal toxemic syndrome appearing when there is impending fetal death because of iso-immunization has been described (21). The characteristic clinical findings of preeclampsia develop, but in addition there may be hydramnios and generalized pruritis.

#### MATERNAL PATHOLOGY

Half of the maternal mortality associated with toxemia (preeclampsia-eclampsia) of pregnancy is due to conditions other than this syndrome proper, such as abruptio placenta, hypofibrinogenemia, pre-existing hypertensive cardiovascular disease, anuria, pituitary necrosis and adrenal necrosis. Of the deaths directly due to toxemia, 60 per cent occur in true convulsive eclampsia, 20 per cent in toxemic collapse, 10 per cent in toxemic coma and 10 per cent in primary cerebral hemorrhage (22). Convulsions are not a prerequisite for fatality.

In some toxemic collapse there is shock at the time of delivery without apparent cause in a patient with mild or severe preeclampsia. Death follows from several minutes to four hours. Clinically there is occasionally some suggestion of amniotic fluid embolism. All such cases show toxemic glomerular lesions, and two thirds have toxemic hepatic lesions. Subendocardial hemorrhages are present if death was delayed at least two hours.

Toxemic coma, the transition of a severe preeclamptic to a state of coma without convulsions, is followed by death in from several hours to several days. The pathologic changes are the same as found in eclampsia except for the absence of cortical petechiae.

Primary cerebral hemorrhage resembles toxemic coma clinically, the differential diagnosis being made by bloody spinal fluid or at necropsy. There are gross cerebral hemorrhages at the same sites as in eclampsia, and the usual lesions are found in other body sites as well. This shows that toxemia of itself, and not the convulsions, causes cerebral hemorrhages. Fatal cases of toxemia may further exhibit intravascular deposition of fibrin in arterioles and capillaries throughout the body (23).

Of patients who die with true convulsive eclampsia, 75 per cent die within the first two days and the remaining 25 per cent die in the following two weeks from late effects. The eclamptic who dies may lapse into coma and have a marked terminal hyperthermia. One-third of fatal cases have multiple small hemorrhages in the cerebral cortex and may have in addition bleeding into the brain substance. Another third may have single small or massive hemorrhages in the basal ganglia (with or without hemiplegia), in the pons (causing Cheyne-Stokes respiration), and in the subcortical white matter without cortical involvement. Cerebral capillary walls may have fibrinoid changes and contain thrombi. One-third of cases show no cerebral lesions. If the patient recovers after eclamp-

sia there is usually no organic evidence of cerebral damage. Almost every fatal case has a severe, diffuse, hemorrhagic bronchopneumonia. Hepatic lesions are present in  $\frac{3}{4}$  of the patients who die early. Grossly, the liver shows numerous petechiae (or diffuse hemorrhages) on its outer surface, particularly in the right lobe (24). Histologically, there are specific periportal lesions showing hemorrhage and fibrin formation at the base of the liver columns with secondary adjacent liver cell necrosis. Only  $\frac{1}{4}$  of the surviving eclamptics show this lesion on liver biopsy. Very rarely, the right lobe of the liver may rupture spontaneously with resultant right costal margin pain and shock. Immediate surgical intervention is mandatory (25). Characteristic renal glomerular lesions are found. The heart may show subendocardial hemorrhages on the left side of the interventricular septum, often associated with shock and acute cerebral lesions. This is present in  $\frac{2}{3}$  of the cases of early death and in  $\frac{1}{4}$  of the late deaths. There is no obvious gross edema of the brain.

#### THE KIDNEY

The most sensitive pathologic index of toxemia is the renal glomerular lesion (27). All glomeruli are affected equally and in proportion to the severity of the disease. All authorities have agreed that the lesion is characteristic but no two authorities can agree on an exact description. Most authorities favor thickening of the basement membrane (28). At The Mount Sinai Hospital, one hundred pregnant women had renal biopsies which were studied by electron microscopy (14, 14A). Thus, the pathology of the renal glomerular lesion could be established. Three factors combined to reduce the capillary lumen: (1) swelling of the cytoplasm of the endothelial or capillary wall cell, (2) an amorphous deposit in the endothelial cytoplasm and beneath the basement membrane and (3) a marked increase in the number of intercapillary cells. (See Figs. I, II and III). There is no swelling of the basement membrane. The lesion is present in all cases of toxemia, however mild, and even without proteinuria. The lesion persists until evacuation of the uterus in spite of apparent clinical improvement with therapy. By nine days postpartum most of the lesion has cleared. The lesion accounts for the characteristic decreased glomerular filtration rate in toxemia. It is not found in normal pregnancy or in otherwise uncomplicated essential hypertension and it appears when there is superimposition of toxemia on essential hypertension. This lesion is the only reliable laboratory manifestation which can identify toxemia and separate it from otherwise uncomplicated essential hypertension in pregnancy. The severity of the lesion may have prognostic significance for the fetus. Aside from providing data on the course of toxemia, renal biopsy can identify chronic renal disease or negate its presence. In multiparous women with the label of clinical preeclampsia or eclampsia in one or more previous pregnancies, renal biopsies have demonstrated a high incidence of unsuspected renal disease (nephrosclerosis, chronic renal disease, chronic pyelonephritis, and lupus nephritis) (29). Since antecedent renal disease may present as, or predispose toward toxemia, it must be considered in any atypical case or in patients with repeated episodes of preeclampsia.

Acute anuria or oliguria may occur as an unusual complication of toxemia.



Transient anuria of several hours duration may occur with brief acute circulatory failure. Prolonged anuria may follow severe renal ischemia causing "tubular necrosis" after two or three hours and "renal cortical necrosis" of varying degrees of severity after six to eight hours of such ischemia. Renal pathology in prolonged anuria is proportional to the severity of the ischemia (30). Clinically it may not be possible initially to ascertain the extent of renal damage nor the prognosis for recovery.

Originally renal function studies in toxemia were compared with inadequate normal pregnancy controls. Subsequently it was appreciated that in normal

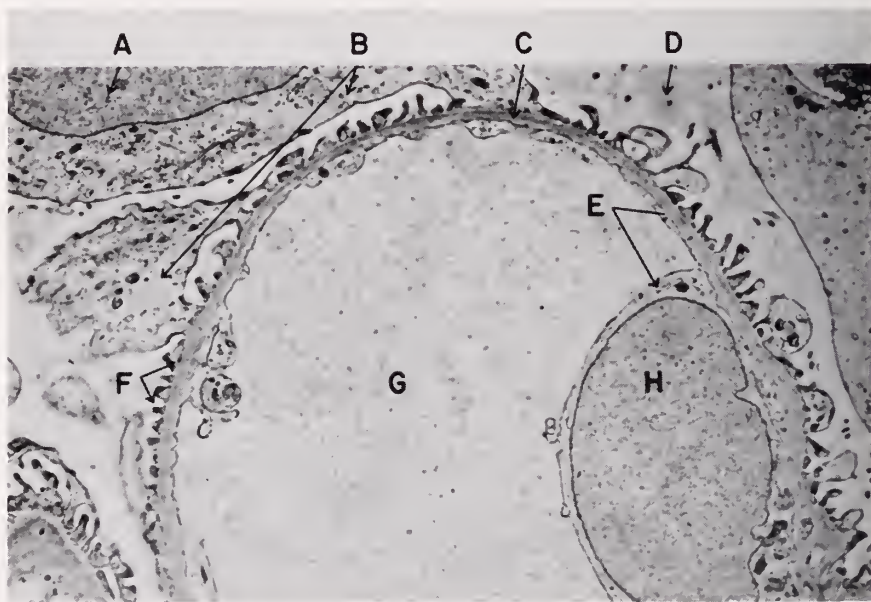


FIG. 1. Renal Biopsy from a normal pregnant woman viewed by electron microscopy  $\times 8000$ . The glomerular capillary loop is normally patent. A, epithelial cell nucleus, B, epithelial cell cytoplasm, C, basement membrane, D, Bowman's space, E, endothelial cell cytoplasm, F, foot processes of epithelial cell, G, capillary lumen, H, endothelial cell nucleus.

pregnancy there are changes in renal hemodynamics (31). A 25 to 50 per cent or more rise in renal plasma flow (measured by para-aminohippuric acid clearance) develops by the beginning of the second trimester and returns to the nonpregnancy level of 600 cc per minute in the last trimester. The glomerular filtration rate measured by inulin clearance is maintained at fifty per cent above the nonpregnancy level of 120 cc per minute throughout the second and third trimesters and does not decrease until delivery. Therefore the filtration fraction tends to be low in early pregnancy, rises towards the usual value in midtrimester, and exceeds its nonpregnancy value by almost fifty per cent in the last trimester. It is assumed that increased tubular reabsorption balances the maintained increased glomerular filtration of the last trimester. In preeclampsia there is a selective reduction in glomerular filtration rate to almost fifty per cent

of normal pregnancy (back to the normal nonpregnancy level). Renal plasma flow decreases to a lesser extent, in inverse relation to the diastolic blood pressure elevation. In severe cases, both may be depressed even below the nonpregnancy levels. Since the renal fraction of cardiac output tends to decrease, renal vascular resistance is relatively increased. Within two weeks after delivery the glomerular filtration rate returns to the usual nonpregnancy value but renal plasma flow returns toward normal values more slowly (32). These studies suggest that there

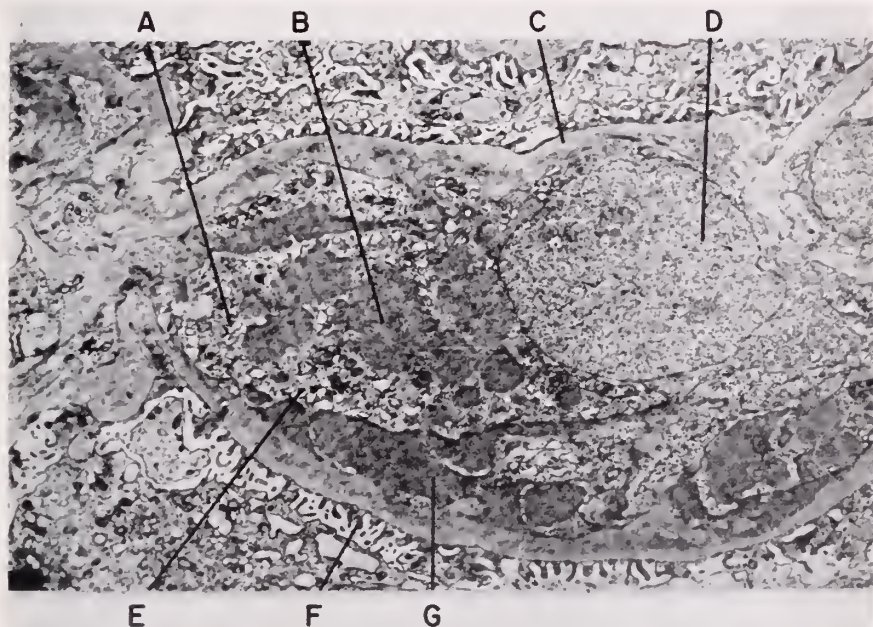


FIG. 2. Renal Biopsy from a pregnant woman with preeclampsia viewed by electron microscopy  $\times 8000$ . The glomerular capillary loop is occluded by swelling of endothelial (capillary wall cell) cytoplasm and a deposit both within the endothelial cytoplasm and underneath the basement membrane (between the endothelial cytoplasm and basement membrane). Previous inadequate magnification by light microscopy caused incorrect interpretation of the findings as swelling or thickening of the basement membrane. A, obliterated capillary lumen, B, deposit in endothelial cell cytoplasm, C, basement membrane of normal thickness, D, endothelial cell nucleus, E, swollen endothelial cell cytoplasm, F, normal epithelial foot processes, G, deposit under basement membrane.

is no permanent renal damage after preeclampsia and that the disease may be viewed as an exaggeration of the normal tendency towards vasoconstriction of the third trimester. A renal mechanism for fluid retention in preeclampsia is suggested by the decreased glomerular filtration rate and increased tubular reabsorption of sodium (33). Decreased renal excretion is the cause of hyperuricemia in preeclampsia (34). Proteinuria may vary hourly.

#### FUNCTIONAL CHANGES

In the midtrimester of normal pregnancy there is a trend toward decrease in blood pressure, perhaps because the placenta acts as an arteriovenous shunt.



Blood pressure returns toward its original level near the end of pregnancy. Preeclampsia represents an exaggeration of the increased last trimester arteriolar resistance which is found in normal pregnancy. Blood pressure elevations in preeclampsia-eclampsia are only moderate as compared to the possible higher levels of essential hypertension. Cardiac output normally rises to a maximum of seven

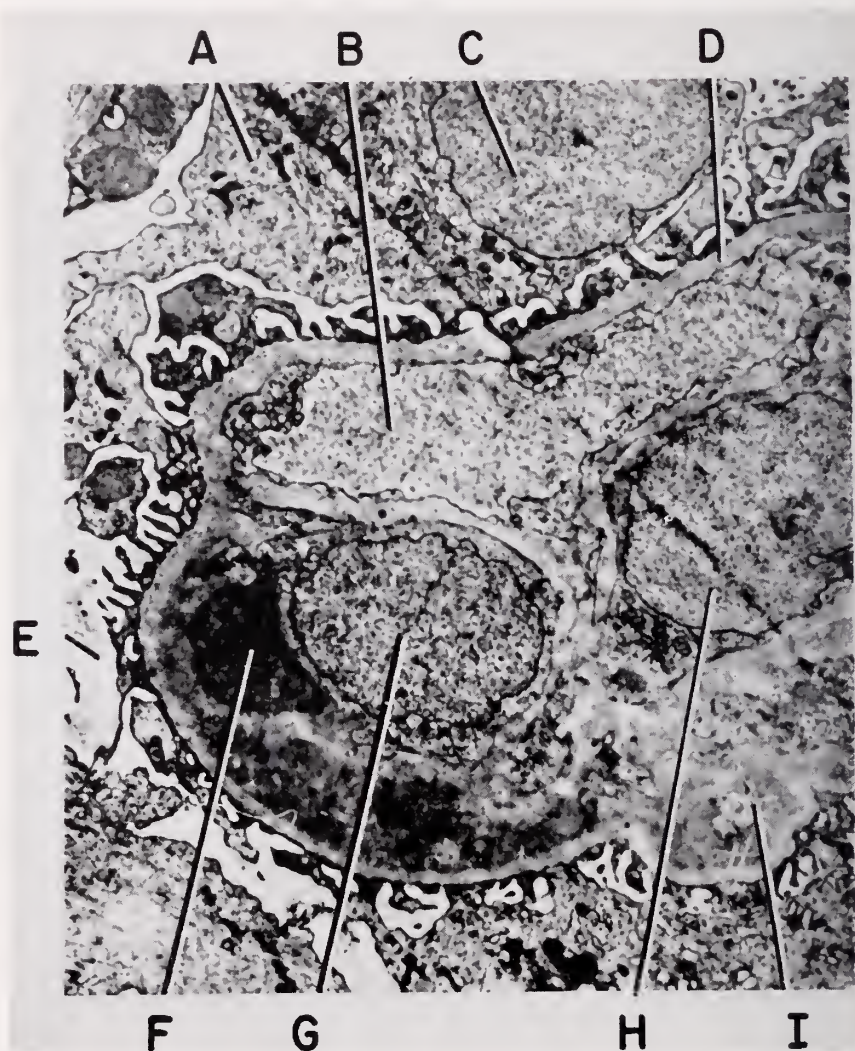


FIG. 3. Renal Biopsy from a pregnant woman with preeclampsia viewed by electron microscopy  $\times 8000$ . The glomerular capillary loop is occluded in part by a great increase in the number of intercapillary cells. These cells burst their boundaries from between capillary loops to encroach on capillary lumen space. The function of these cells is unknown and their very existence was previously generally denied. A, epithelial cell cytoplasm, B, capillary lumen reduced in size, C, epithelial cell nucleus, D, basement membrane of normal thickness, E, normal epithelial foot processes, F, dark staining deposit in endothelial cell cytoplasm, G, and H, nuclei of intercapillary cells, I, light staining deposit in endothelial cytoplasm.

liters per minute during the 25th to 27th weeks of gestation and then gradually falls toward the prepregnant level of 5.5 liters per minute. Plasma volume reaches a maximum of about 25 per cent increase in the 28th to 33rd week. There is a fall in plasma volume in the two weeks prior to delivery. Plasma volume is unchanged in mild preeclampsia but may be reduced in severe preeclampsia-eclampsia. Preeclamptic women over-react to pressor substances and there is increased vascular reactivity even before the development of preeclampsia (11).

In normal pregnancy there are quantitative alterations of plasma protein consisting of reduction of concentrations of total protein, decrease in albumin/globulin ratio, decrease in albumin, and gamma globulin; and increased concentrations of alpha 1 and alpha 2 globulin and fibrinogen. In preeclampsia-eclampsia the changes in plasma protein are largely exaggerations of the changes of normal pregnancy (35).

Preeclampsia may cause a decrease of between 25 to 50 per cent of the normal uteroplacental blood flow of 600 ml per minute. Although antihypertensive drugs may increase blood flow while reducing systemic hypertension, nevertheless antepartal fetal death may occur (36). Uterine blood flow as determined by the clearance rate of radioactive sodium injected into the myometrium, while reduced in preeclampsia, is further depressed by exercise and postmaturity (37). It may be independently reduced by marked edema, twin gestation, postural hypotension, vaginal bleeding, maternal infection and in labor by frequent and long contractions and by prolonged labor. Decreased placental function in preeclampsia is suggested by the reduction of the normal 1.65:1 ratio of fetal to maternal plasma amino acid levels. There appears to be a diminished oxygen pressure of maternal placental blood in preeclampsia (38).

Cerebral vascular resistance markedly increases in toxemia of pregnancy, although the normal cerebral blood flow of 54 to 56 ml per 100 Gm per minute is maintained. Eclamptic convulsions are considered the result of vasospasm and may be a reflection of pre-existing cerebral dysrhythmia as well as the severity of the toxemic process. In eclamptic coma there is a significant depression of cerebral oxygen metabolism and cerebral blood flow is decreased to 51 cc (39).

The slight arteriolar spasm in the ocular fundus occasionally observed in the third trimester of normal pregnancy becomes markedly accentuated in preeclampsia. Hypertensive retinopathy may develop, but hemorrhages and exudates are very unusual. Increase of retinal arteriolar diastolic pressure has been recorded even prior to peripheral pressure rise. In preeclampsia the bulbar conjunctiva may develop ischemia, diffuse capillary tortuosity, and rarely petechial hemorrhages and thrombi (40).

Normal pregnancy increases finger circulation by decreasing neurogenic vasoconstriction thus increasing heat loss. There is a decreased systolic brachial-digital pressure gradient. Elevation of systemic blood pressure of toxemic patients in the last trimester results in some increase in digital neurogenic vasoconstriction, an increase in systolic and diastolic brachial-digital arterial pres-



sure gradients, but no change in the digital blood flow (41). Generalized decrease of skin or muscle blood flow has not been found in preeclampsia.

In preeclampsia, rapid weight gain and edema result from accumulation of excess extracellular extravascular fluid of normal electrolyte composition. The cause is unknown but the method of execution is through the kidneys.

The validity of many physiological studies of fluid retention in toxemia of pregnancy has been questioned because:

1. The physiology of the normal pregnant woman is uncertain, and probably changes as the pregnancy progresses.
2. The diagnosis of causes of hypertension in pregnant women is difficult, and therefore the clinical label not always correct.
3. Methodology is crude and reproducibility of results as well as detection of significant differences is difficult.
4. Studies may be made in different phases of the natural course of the disease and in different phases of therapy.

For example, the role of the aldosterone hormone was immediately considered in toxemia as soon as the hormone was discovered. Statistically, pregnant women with toxemia had more aldosterone in the urine than normal pregnant women. Aldosterone, however, was simply fulfilling its physiological role of being present in increased amounts when the patient was on a low salt diet in order to prevent salt depletion. Clinically, the preeclamptic has more sodium and water retention (or at least slower excretion) than the normal pregnant woman who in turn retains more than the nonpregnant. Balance studies in normal pregnancy and preeclampsia indicate that salt and water are neither retained nor excreted in the same concentration as in extracellular fluid (140 mEq of sodium per liter water). More salt than water is absorbed by the pregnant woman, whereas more water than salt is lost in diuresis (42). This suggests that salt is kept in the body in an osmotically inactive area, perhaps bone or some intracellular site. Radioactive sodium tracer studies in toxemia have given contradictory results with reference to mean total exchangeable body sodium (43, 44), possibly reflecting the differences between untreated and treated cases. Corticosteroid urinary excretion in toxemia is not abnormal. Antidiuretic activity has been allegedly demonstrated in preeclamptic plasma in proportion to the severity of the toxemia (45) and in preeclamptic serum and in normal pregnancy serum, and is inactivated by normal pregnancy plasma (46). The urine of preeclampsics is reported to contain antidiuretic hormone in increased amounts (45). Unfortunately, the methods employed are of controversial reliability.

Suggestions of metabolic changes in preeclampsia include slightly decreased tolerances to glucose and fructose (47) and increased plasma pentose and serum transaminase (48).

#### THE PLACENTA

The severity of toxemia cannot be precisely correlated with pathologic findings in the placenta for the individual case. There is a tendency towards "premature aging", with syncytial degeneration leaving a thin hyalinized non-nucleated

villus surface, fibrin replacement, reduction of intervillous space, ischemia, necrosis and infarction. The syncytium is comparable to an endothelial lining and when intact prevents fibrin deposition. Placental injury or infarcts result from decreased nutritive maternal blood flow due to decreased uterine blood flow or acute atherosclerosis of the decidual spiral arterioles (49) or abruptio placenta. Seventy-five per cent of placentas with ten per cent or more infarcted area, are associated with preeclampsia or abruptio placentae. Uncomplicated essential hypertension does not share the same tendency towards infarcts. Infarction of over thirty per cent of the placenta is associated with stillbirths. The concept of the placenta having an unused functional reserve margin of safety seems to be incorrect, inasmuch as infarction has been statistically correlated with increased fetal mortality, fetal distress, placental coefficient and decreased newborn term weight (50). Low birth weight in relation to gestational age occurs in severe preeclampsies with proteinuria who deliver prematurely. The placental weight in such cases is less affected than the fetal weight (51).

The standard method of analyzing newborn results is by perinatal mortality, which is a combination of the stillbirth rate and neonatal death (newborn death) rates. "It can be estimated conservatively that at least 30,000 stillbirths and neonatal deaths each year in this country are the result of toxemia of pregnancy" (7). Most perinatal mortality in toxemia is the result of silent antepartum death of the fetus in the uterus, apparently the result of gradual placental failure. The next largest category of perinatal mortality in toxemia is stillbirth due to premature separation of the placenta (abruptio placentae). Clinically this accidental hemorrhage is increased in toxemia to 1:18.3, compared to an incidence of 1:133 in normotensive pregnancies (52). The more severe the disease, the greater the possibility of abruption, particularly with massive central separation and rapid fetal demise. Since the fetus in these cases tends to have a normal birth weight, this implies adequate placental function until an acute episode supervenes. Pathologically there is decidual hemorrhage, necrosis and degeneration due to vascular change. Old or recent placental infarction is often present in "toxic" separations. Experimental abruptio placentae has been produced by occlusion of the inferior vena cava in dogs and in two normotensive women. The "supine hypotensive syndrome" caused by compression of the inferior vena cava by the pregnant uterus might be a factor in placental abruption.

Autopsy investigations of perinatal deaths do not reveal any significant etiological data in relation to toxemia unless the maternal situation is carefully investigated. There is no pathognomonic sign of toxemia on post mortem study. Even when perinatal death is directly attributable to toxemia the only pathological findings are the nonspecific ones of maceration, prematurity, or the effects of anoxia; or there may be no pathological finding. A review of 407 cases of fetal deaths before the onset of labor disclosed that toxemia as a direct cause together with toxemia associated with abruptio placentae represented 31 per cent of the cases and was the largest etiological factor (53). The smallest percentage of perinatal mortality is in neonatal deaths. Usually if a baby is born in reasonable

condition and is not too premature it will survive. The approximate overall perinatal mortality in preeclampsia is 5.5 per cent, in essential hypertension 6.3 per cent, in eclampsia 11 per cent, and in preeclampsia superimposed on essential hypertension 19 per cent (6).

#### LONG TERM EFFECTS IN CHILDREN

In retrospective studies, toxemia of pregnancy has been statistically incriminated as one of the significant factors (other factors include prematurity and vaginal bleeding) in intrauterine life and birth which causes a "continuum of reproductive casualty". The lethal component represents abortions, stillbirths and neonatal deaths. The sublethal components include cerebral palsy, epilepsy, mental deficiency, reading disorders and behavior disturbances in children (54). Another interpretation of cerebral palsy is that prematurity is the transcending factor, and that toxemia appears because it is associated with prematurity (55). One difficulty in establishing relationships is that disturbances in cerebral function cannot be revealed by examination of the newborn. Another problem is that each of these disturbances may have many possible causes.

#### GENERAL PRINCIPLES AND PREVENTIVE MANAGEMENT

One of the most important functions of prenatal care is an attempt at prevention or early identification and modification of toxemia of pregnancy. It is generally agreed that eclampsia, that is the convulsion itself, is preventable, but that preeclampsia (even though statistically reducible) is not preventable. Patients are encouraged to make their first prenatal visit as soon as possible, or better yet to have a general health evaluation prior to pregnancy. The usual frequency of visits during prenatal care is once monthly for the first 24 to 48 weeks, then every three weeks and finally weekly for the last four weeks. Although this schedule may be admirable for the average patient, the frequency of visits for patients who are candidates for toxemia or who have pre-existing hypertensive or renal disease, should be increased preferably to no longer than two week intervals. At the first prenatal visit the following should be noted: weight, blood pressure, eye grounds, urine analysis and hemoglobin.

If renal disease is suspected some suggestive procedures are: a urine concentration test; blood for urea nitrogen, creatinine and uric acid; phenol-sulfonephthalein test; serum electrolyte studies; and endogenous creatinine clearance. More exact renal studies involve determination of glomerular filtration rate and renal plasma flow. The speed of dye appearance and its intensity on an intravenous pyelogram gives a measure of tubular secretory function, although this procedure is usually avoided during pregnancy unless the possibility of surgical urological disease exists. Unilateral renal disease may be suspected because of severe hypertension, especially of sudden onset, in a young woman with a history of back pain and hematuria. To verify such suspicion, possible diagnostic tests include examining the secretory activity of each kidney separately by ureteral catheters, a single film two minutes after injection for intravenous pyelography, radioactive diodrast renography and renal angiography.

Further routine visits include weight, blood pressure and urine for protein and sugar. The average patient is instructed at the first visit to keep her weight gain for the entire pregnancy at twenty pounds. With the total length of pregnancy of forty weeks, this gives an overall average weight gain of one-half pound per week. Weight gain of over one pound weekly suggests fluid retention even though there may be no clinical evidence of edema at that time. In those cases which are suspect, patients should be advised to attempt to limit weight gain to ten pounds. Patients who are obese at the onset of pregnancy are actually instructed to lose weight during the course of the pregnancy. In spite of the weight loss the parturient and newborn still enjoy good health. Patients are to be reassured that the size of the baby is essentially unrelated to the weight gain or loss, other factors being equal, and that the fetus has first call on maternal nutrition. All patients at the first visit are generally encouraged toward a high protein, low calorie, low salt diet with the strictness of enforcement dependent on the individual case. Unlimited food intake, aside from excess calories, also increases salt intake. Of course some patients in early pregnancy complain of nausea and vomiting, and these patients at that time should not be forced to eat certain foods lest bouts of emesis be precipitated.

Water intake is not restricted. The average patient may ingest five to ten Gm of salt daily. In spite of careful directions to the patient, the actual salt intake on a theoretical low salt diet may be two to five Gm daily. A really low salt diet of 200 to 800 mg daily can be achieved only by a hospital diet kitchen. Strict and frequent observation of the patient offers the best insurance against dietary indiscretion.

Most pregnant women require dietary supplementation of iron because of inadequate stores and increased requirement. Previously this was considered the only supplement necessary. Recent laboratory studies illustrating selective fetal absorption of certain B vitamins and amino acids, together with suggestions of placental insufficiency in certain cases of toxemia suggest prenatal vitamin supplements.

The normal pregnant woman may maintain her occupation during pregnancy providing she lives in moderation. For the toxemic patient, however, rest is of significant therapeutic value. Bed rest alone may eradicate the symptoms of preeclampsia in several days, producing a negative salt and water balance, clearance of edema, weight loss, reduction of blood pressure and even subsidence of proteinuria. This may involve improvement in renal and hepatic blood flow and reduction of aldosterone and norepinephrine secretion. Women with essential hypertension or other predisposition to preeclampsia are urged to lie down each afternoon for one hour. Any patient with essential hypertension who wishes to undergo pregnancy must be willing to spend variable periods of time at rest, particularly in the last trimester. Hospital beds must be readily available at all times for antepartum patients with toxemia. In addition to adequate rest, mild sedatives such as phenobarbital 15 to 30 mg three times daily are often prescribed for the predisposed patient.

Aside from diet and rest, another factor in preventive management is the



liberal use of diuretic agents. Because of the limited efficacy of diet in achieving a negative salt balance, diuretics have fulfilled a vital role. The most frequently used and safest agents are meralluride, acetazolamide and chlorothiazide. Hydrochlorothiazide, trichlormethiazide, and hydroflumethiazide and benzhydroflumethiazide are some of the more recently available diuretics. These agents should be used intermittently for maximal benefit and minimal toxicity. With continuous use of any diuretic the sodium excretion effect tends to fall as salt depletion is achieved. The glomerular filtration rate may be reduced and may further limit salt excretion, and there may be increased potassium loss in the urine. Potassium loss is common in all patients who are sodium retainers when intensive diuretic therapy is imposed. Therefore, intermittent therapy for two or three days with similar interposed rest periods is recommended, especially if diuretic therapy is necessary for several weeks or months. In addition, for continued therapy it is advisable to administer supplemental potassium on rest days of 60 to 80 mEq daily. This corresponds to four to six teaspoons of potassium citrate which contains 15 mEq per teaspoon, or three to four tablespoons of potassium gluconate containing 20 mEq per tablespoon. The efficiency of any diuretic should be measured by the weight loss obtained. Relative resistance to one agent may require a change to another. Meralluride is an effective diuretic given as 1.5 to 2.0 cc intramuscularly. Its effectiveness is enhanced by acidification for three days previously by 10 Gm of ammonium chloride syrup together with acetazolamide. Meralluride may be cautiously used even in the presence of heavy proteinuria. Acetazolamide is prescribed as two tablets daily each containing 250 mg.

Chlorothiazide is an effective diuretic. The daily dose is 500 to 1000 mg for two or three days. A mild antihypertensive effect may be observed in uncomplicated essential hypertension especially if the patient is receiving a ganglionic blocking agent. In preeclampsia and in the normal pregnant woman there is no hypotensive effect. Although an effective diuretic, chlorothiazide does not reverse the toxemic process as evidenced by fetal loss and incidence of small babies. Diuretics and antihypertensive drugs can reverse edema and blood pressure elevation and without those clinical signs, reduced rate of fetal growth and proteinuria may be the only evidences of further advancement of the toxemic process (56). The most important side effect of chlorothiazide is reduction of blood potassium and extracellular alkalosis due to excess excretion. Hypokalemia may cause muscle weakness or paralysis and may predispose patients with heart disease to cardiac arrhythmias and digitalis toxicity. It is possible that chronic hypokalemia may cause renal damage. Hepatic coma and ammonia intoxication may be produced in cases of severe liver disease. There may be a low salt syndrome with weakness and emesis. It increases blood uric acid and can provoke an attack of gout. Neutropenia, thrombocytopenia and serious allergic reactions have been reported. Nevertheless, chlorothiazide continues to be the most extensively used diuretic since it is usually effective, relatively safe and easy to administer. Hydrochlorothiazide, the dosage of which is ten per cent of chlorothiazide would seem to have properties similar to those of the latter.

Using diet, rest, mild sedation and diuretics about 85 per cent of toxemia patients can be controlled. Mildly ill patients and those with pitting edema developing in a short time usually respond well to hospitalization under this simple regime. Such patients are apparently cured of preeclampsia after several days and may be discharged to be carefully observed once or twice weekly.

#### THE ACUTELY ILL PATIENT

Sometimes the pregnant woman presents herself late in gestation without previous prenatal care and with apparently sudden marked edema, severe hypertension and proteinuria. The need for immediate therapy is further emphasized by signs of impending eclampsia such as severe headache, epigastric pain or muscular irritability. As soon as the patient is seen she must be hospitalized and sedated. She is gently placed in a quiet, dark room, the blood pressure and extent of edema determined, a catheterized urine specimen obtained (catheter left indwelling), and the degree of hyperreflexia checked. These are the criteria for the initial impression. In the milder cases, phenobarbital in doses of 30 to 60 mg every four to six hours may be sufficient. For more severe cases morphine, 15 mg is given intramuscularly at once, and it is usually not necessary to repeat. Magnesium sulfate is usually administered to prevent convulsions. It also has a mild hypotensive effect and tends to increase cerebral blood flow. The initial dose is 10 Gm given as 10 cc of fifty per cent solution by careful, deep intramuscular injection into each buttock. Subsequent doses (given for hyperreflexia to prevent convulsions) are 5 Gm every six hours. Before each dose it must be ascertained that deep tendon reflexes are present and that there is no oliguria (at least 200 cc of urine in six hours) since its excretion is by the kidney. The antidote of the respiratory depression of magnesium toxicity is 10 cc of ten per cent intravenous calcium gluconate which should be kept available. Once sedation and magnesium sulfate have been administered, convulsions are extremely unlikely. Meralluride 2 cc intramuscularly is given for diuresis. The patient is handled with care and watched cautiously.

Hypotensive (antihypertensive) drugs have been used by us only to control hypertensive crises which arise in spite of sedation. It is to be remembered that there may be marked differences in reaction among patients to similar medications and that tolerance may develop. Some patients may have a delayed reaction and with continued use of a drug, go into shock. There are many possible methods of administration and combinations, but all are empirically used to reduce the brachial blood pressure. Whichever drugs are utilized, blood pressures should be recorded every five minutes for the first hour and thereafter every fifteen minutes. The drugs most often used are:

- (1) the veratrum derivatives (each with its separate dose schedule)
- (2) hydralazine hydrochloride
- (3) reserpine

Protoveratrine A and B in doses of 2 mg in 200 cc of 5 per cent dextrose in water solution by intravenous infusion or 0.2 to 0.6 mg intramuscularly every four to six hours may be used to reduce the blood pressure to about 150-160/90-

100 mm. The pressure is not reduced to normal levels and if very high, only a 25 per cent reduction is proper. This drug produces a moderate bradycardia and a sensation of warmth throughout the body. Ephedrine 25 mg and atropine 0.4 mg are kept available for intravenous administration to counteract severe hypotension or bradycardia. Veratrum derivatives may increase cardiac excitability and the use of this agent in patients who have been digitalized is hazardous since arrhythmias may occur. Symptoms of overdosage are progressive nausea, vomiting, hypersalivation, severe bradycardia, hypotension and collapse. Again it must be emphasized that there are many veratrum derivatives, each with its own separate dose schedule and the manufacturer's recommendations must be carefully studied.

Another method is a vasodilating infusion of 20 mg of hydralazine and 5 mg of veratrum viride in 500 cc of 5 per cent glucose in water as an intravenous drip (57).

Hydralazine may also be given separately in dosage of 20 to 40 mg intravenously slowly and directly, or in a 500 cc intravenous drip. Tolerance to the drug may develop when used alone after several injections. It usually produces a remarkable fall in blood pressure, but less dramatic in essential hypertension without preeclampsia. Hydralazine increases renal plasma flow and decreases renal resistance while glomerular filtration rate either remains the same or decreases slightly. The urine flow shows some reduction at the onset of the blood pressure fall but returns to normal shortly thereafter. Cerebral blood flow and metabolism are increased and cerebral vascular resistance decreases. Side effects of hydralazine include tachycardia, headaches, nausea and vomiting, drowsiness, feeling of warmth and throbbing of the head. Manifestations of collagen diseases have also been reported after prolonged treatment with large oral doses (58).

Reserpine is usually used by the oral route for gradual, mild reduction of hypertension and gentle sedation. The daily doses are 0.5 mg for a week and then reduction to 0.25 mg or less for maintenance. It is also supplied in ampules as 2.5 mg per ml. Some authorities give 5 mg intravenously as an antihypertensive agent alone or to augment the activity of other drugs (59).

Patients admitted with convulsions or coma present an even more serious problem. It is essential to stop the convulsions and stabilize the patient's clinical condition. Previously mentioned therapies of sedation, magnesium sulfate, diuresis, and antihypertensive drugs (if necessary) are utilized. In addition, there must be continual observation of the patient in her quiet private room with the following supportive measures available: special nursing care, continual recording of blood pressure at least every half hour, oxygen by nasal catheter, suction apparatus, mouth gag, oropharyngeal airway, indwelling catheter to record hourly urine output, tracheotomy set for nasopharyngeal obstruction, padded side rails, intravenous infusions of 5 or 10 per cent glucose in water (1000 cc more than prior 24 hour urine output, up to 2400 cc daily), rotating tourniquets to treat pulmonary edema, and broad spectrum antibiotics to prevent bacterial pneumonitis. The patient may be digitalized prophy-

laetically or at the first sign of cardiac failure. Once convulsions have stopped and the patient's condition is stabilized for 24 hours, it is proper to terminate the pregnancy promptly by whatever obstetric means prove the most feasible. Cesarean section or induction of labor when convulsions are just ended or about to begin has a high mortality. Often the patient will solve her own problem and go into spontaneous labor the day after the convulsions. Pituitrin in an intravenous drip as 1 cc in 1000 or 500 cc of 5 per cent glucose in water is administered to start labor with a favorable cervix for induction and amniotomy. The patients are kept well sedated during labor, are permitted only a short second stage and are delivered under general or local anesthesia. Spinal or caudal anesthesia is avoided because of possible drops in blood pressure. To avoid depression of respiration in the newborn, n-allyl-normorphine 5 to 10 mg is given intravenously to the mother ten minutes before delivery. The only oxytocic used in the puerperium is pituitrin, since ergot derivatives may elevate blood pressure. If induction of labor is not prompt or the condition of the cervix unfavorable Cesarean section is performed. Uterine evacuation after eclamptic convulsions is done to preserve the life of the patient. Some institutions have recently suggested carrying a pregnancy after convulsions have been controlled using antihypertensive drugs until the fetus is of viable size (59). This policy is not in accord with usual practice. Furthermore the fetus may still die in spite of increased uterine blood flow as experimentally observed in six patients.

#### THE INDIVIDUAL PROBLEM PATIENT

A difficult decision is presented by a patient whose hypertension and proteinuria persist and whose fetus is still not of viable size. What constitutes viability? The usual criterion for ability to survive outside the womb is 1000 Gm weight or 28 weeks gestation. In the weight range 400-999 Gm based on overall averages, the perinatal mortality is 96.6 per cent (60). In 500 Gm increments, perinatal mortality starting at 1000 Gm drops to 66.1, 22.1, 6.3, and 1.0 per cent of 2500 Gm and over newborns. Once the fetus weights 2500 Gm or more (36 weeks or over gestation) there is a 99 per cent chance of survival. At 32 weeks gestation (1700 Gm) perinatal mortality is 22.1 per cent, or survival is 77.9 per cent. Thus we note a sharp increasing gradient in survival based only on size-date factors from 28 to 36 weeks.

Since manifestations of preeclampsia can be eliminated by evacuation of the uterus, the question of interrupting pregnancy arises when the usual therapy has failed. The factors to be considered are:

1. Is the perinatal loss greater by termination of the pregnancy in a given week or by delaying termination?
2. The clinical signs of the patient's disease.
3. The danger to the patient.
4. The patient's anxiety for the pregnancy.
5. The past obstetrical history.

If the patient is 36 weeks or more gravid (and the fetus 2500 Gm or over) there is no problem. Such a patient should have an induction of labor. Preg-



nancies less than 36 weeks represent the difficult questions. Placental function unfortunately can not be routinely measured. Clinically continued growth of the uterus measured by height above the symphysis pubis, and increase in the size of the fetus implies adequate placental function, but such estimates are crude. Maternal perception of fetal activity, although suggestive, cannot be used as a guide. The age of the fetus in relation to prematurity suggests intra-uterine life be continued for at least 33 weeks before evacuation is considered. Persistent moderate or marked elevation of diastolic pressure associated with 2+ or more proteinuria is an indication for emptying the uterus any time after the 33rd week, especially after a week of good hospital management. A history of recurring perinatal loss or stillbirths and placental failure or pre-existing essential hypertension are all ominous signs for the newborn. There appears to be less danger for the patient in continuing the pregnancy than was previously thought. It is uncommon for a patient under hospital care to suddenly worsen or develop impending eclampsia or heart failure, and if these occurred the uterus would be evacuated. Renal failure does not generally appear unless there is pre-existing renal disease, eclampsia or cortical necrosis, or acute renal insufficiency caused by blood loss and hypotension. It is true, however, that progressive retinopathy with exudates and hemorrhages demand uterine evacuation lest blindness occur. It is the current view that hypertension persisting after delivery means that hypertension or a "hypertensive diathesis" existed prior to pregnancy. Even though statistically, the presence of preeclampsia for three or more weeks prior to delivery is associated with post delivery hypertension, it simply implies that the patient with essential hypertension developed resistant superimposed preeclampsia relatively early in pregnancy. Preeclampsia is not thought to cause hypertension after pregnancy (61). It is true that re-examination of women many years after their preeclampsia shows an increased incidence of essential hypertension. This has been interpreted to mean that the patient who develops preeclampsia is predisposed towards vascular disease to begin with. Willingness to continue a pregnancy in a mother whose health or life is threatened by specific toxemia is less if there are several living children already. On the other hand, in elderly primiparas who want a living child, it may be decided not to terminate the pregnancy until fetal viability can be achieved.

#### ESSENTIAL HYPERTENSION

The goal of therapy in such patients should be to maintain the blood pressure as close to normal as possible throughout the pregnancy, and to prevent the development of a superimposed preeclampsia. These patients must be maintained on a strict salt-free diet throughout pregnancy and total caloric intake kept at a minimum so that the weight gain does not exceed twenty pounds; preferably it is kept below ten pounds. Diuretics may be used at intervals and potassium depletion should be prevented by administration of potassium in doses of 60 to 80 mEq per day for three consecutive days at similar intervals. Antihypertensive drugs are often of value in conjunction with the previous measures. The daily administration of Rauwolfia derivatives, occasionally in association with hydrazine, may be necessary to maintain blood pressure at

reasonable levels. During the last trimester, precautions must be exaggerated. Patients must be observed at very frequent intervals for the detection of sudden weight gain or edema, increase in blood pressure, or albuminuria. The therapy mentioned above must often be intensified if any such manifestation develops. Intervals of bed rest and even hospitalization are often necessary to cope with the development of any manifestations of superimposed preeclampsia. It is reassuring to note how frequently such patients can be carried to term and through labor without any evidence of superimposed preeclampsia. As soon as it appears that a full, viable birth is possible, generally after 36 to 37 weeks of pregnancy, evacuation of the uterus should be considered by whatever obstetric means seem feasible, especially if any evidence of superimposed preeclampsia develops. This group must be watched with extreme care during labor. At this time, preeclampsia or eclampsia may develop; therefore the blood pressure must be followed frequently and meticulously. Antihypertensive agents must be added to the regimen if, during labor, increasing blood pressure develops. Generally the catastrophic fetal effects of placental ischemia will not occur, unless blood pressure rises markedly during the last trimester or unless severe preeclampsia is superimposed. Hypertensive subjects are very vulnerable to blood loss and may promptly lapse into shock if excessive hemorrhage occurs during parturition. Careful and intelligent management of these patients will often produce very gratifying results.

Mild essential hypertension without superimposed preeclampsia offers no additional fetal risk (62). Severe hypertension with diastolic pressures of 110 mm of mercury or more implies a perinatal mortality rate of 20 per cent. Superimposition of toxemia (which occurs in approximately 28 per cent of cases) increases the perinatal mortality markedly. Prolonged oral reserpine therapy (3 mg daily) may retard the development of clinical signs of superimposed preeclampsia until the onset of labor; however, that the disease process continues is reflected in the reduced rate of fetal growth and an unchanged perinatal loss figure (63).

Similar dietary prophylaxis should be instituted in patients with underlying renal disease such as polycystic kidneys or latent chronic glomerulonephritis. If kidney function is good, such patients handle pregnancy well. In regard to patients with previous pyelonephritis, it must be remembered that pregnancy tends to cause obstruction to the flow of urine with consequent hydronephrosis and pyelonephritis, particularly on the right side. For this reason, patients who have a history of recurrent pyelonephritis and who have had a recent attack must be observed carefully. If any sign of infection develops, careful bacteriologic studies must be obtained and the infection treated intensively for at least a seven to ten day period. Since there is justifiable reluctance to perform intravenous pyelograms in the pregnant woman, antibiotic therapy should not be curtailed before complete bacteriologic cure is accomplished.

#### HOW TO ADVISE THE PATIENT

Frequently, patients with a history of previous preeclamptic episodes or underlying hypertensive vascular disease, or both, are anxious to undertake

another pregnancy. The question then arises as to the feasibility of carrying such a pregnancy to viability without imposing permanent damage on the mother. If the history of one or more episodes of specific hypertension of pregnancy is not associated with any clinical evidence of sustained hypertension or vascular disease, future pregnancies need not be interdicted. It is entirely possible, and indeed even likely, for a patient with a prior episode of preeclampsia to undergo subsequent pregnancies without any recurrence of specific hypertensive disease. The best available data suggest that approximately 25 per cent of such patients will develop preeclampsia during a subsequent pregnancy, the remainder showing no evidence of recurrence. It is therefore wise to encourage pregnancies in patients with a history of one or more episodes of prior preeclampsia, provided that there is no evidence of permanent hypertensive disease. Such patients must be followed with careful attention to excessive weight gain, salt retention, or increasing blood pressure. If they are unwilling to follow the prescribed medical regimen, such pregnancies should be discouraged. Furthermore, all concerned must be seriously cautioned about the possibility of recurrent preeclampsia with its attendant dangers, primarily to survival of the baby. As evidence accumulates to suggest that specific hypertension of pregnancy *per se* does not lead to permanent hypertensive disease but rather, reflects an underlying hypertensive diathesis, this leniency regarding future pregnancies appears justified. On the other hand, if the history is one of recurrent pregnancy hypertension associated with multiple episodes of placental failure, the danger of future pregnancies is increased, even in the absence of sustained hypertension in the nongravid state.

Another group in which a similar question regarding future pregnancies may arise, is the group in which sustained hypertension already exists with or without a history of previous preeclampsia. In such patients, many factors must be considered in reaching a decision about the feasibility of subsequent pregnancies. Primarily, the status of the underlying hypertensive process must be precisely evaluated. If the hypertension has progressed to that point where definite involvement of the fundi, heart, or kidneys is evident, subsequent pregnancies should be seriously discouraged. Such involvement may be recognized in the form of arteriolar changes in the eye ground beyond grade I, by evidence of left ventricular strain, either fluoroscopically or electrocardiographically, or by a nephropathy manifested by persistent albuminuria and evidence of reduced renal function. If the diastolic pressures consistently range above 110, or show evidence of sudden rise, this factor should interdict future pregnancies. The level of blood pressure must often be interpreted in the light of knowledge that the patient is receiving mild or potent antihypertensive agents. It is our impression that when the more potent agents are necessary to reduce the blood pressure under nonpregnant conditions, this fact should prohibit future pregnancies. The age of the patient must also be considered. Generally, the older the woman the more frequent the evidence of organ involvement secondary to sustained hypertension. However, if the patient is above 35, essential hypertension even without organ involvement would tend to make future pregnancies undesirable.

Alternatively, the patient may be under thirty, with only mild hypertension; yet the previous obstetric history may include many episodes of placental failure. From the viewpoint of prognosis, such a history would reduce the likelihood of future successful pregnancies, but the patient's own welfare is not sufficiently threatened to interdict pregnancy.

Not infrequently, a patient in her early thirties or even twenties who wishes to become pregnant, presents herself with a mild, sustained, essential hypertension. If the deterring factors listed above are not present, pregnancy may be attempted. The presence of uncomplicated mild hypertension in young women should not be a basis for advising against pregnancy. However, serious and thoughtful discussion with the prospective mother and father must include an appraisal of the attendant risks. In our opinion, these involve primarily the possibility of loss of the infant in the second half of pregnancy. The threat to the mother is very slight. Increasing evidence suggests that the postpartum hypertensive process will return to the levels encountered before the onset of pregnancy. The patient and her family must be made aware of the necessity of meticulous medical care throughout the pregnancy. It must be openly admitted that such women may carry almost to term and then, despite the best care, develop a superimposed preeclampsia with placental insufficiency and severe hypertension. In our experience, this course of events has been quite infrequent if the patient is willing to cooperate fully in maintaining the appropriate medical regimen.

Another group of patients who may wish to become pregnant are those with underlying renal disease of differing etiology. The most common group are young women with a history of diffuse glomerulonephritis. A prior history of acute diffuse glomerulonephritis with complete clinical recovery does not in any way limit the possibility of future uncomplicated pregnancy. On the other hand, if the underlying glomerulonephritis has produced a nephrotic syndrome by the time pregnancy is being considered, pregnancy is undesirable.

Certainly any degree of detectable renal insufficiency precludes permission to attempt pregnancy. Latent chronic glomerulonephritis manifested only by persistent mild albuminuria does not afford adequate reason for forbidding future pregnancies. Such patients may have a remarkably good prognosis, sometimes with ultimate disappearance of the albuminuria. Furthermore, in our experience, this group does not have a measurably enhanced likelihood of developing superimposed preeclampsia.

Occasionally, patients seek permission to become pregnant who have in the past been subjected to a nephrectomy. If the remaining kidney is normal, this group may undergo normal pregnancy. It has not been our experience that patients with one remaining kidney show a higher incidence of preeclampsia. Patients with previous pyelonephritis may be permitted to undertake pregnancy provided renal function is normal, and no evidence of obstructive uropathy or conspicuous hydronephrosis exists.

Patients with congenital polycystic kidneys pose a special problem. Often these women are not aware of their disease in their early childbearing years and



undergo normal pregnancies without renal complications. If an opportunity presents itself to advise such a patient before pregnancy, the possibility that the disease will develop in the offspring must be frankly explained. If renal function is good, however, such patients usually have successful and uncomplicated pregnancies.

In recent years, coincident with improvement in the management of patients with hypertensive and renal disease during pregnancy, these conditions less frequently necessitate therapeutic abortion. The indication for a therapeutic abortion is the likelihood that continuation of pregnancy will cause permanent maternal damage or threaten life. With the accumulation of evidence indicating that specific hypertension of pregnancy does not, *per se*, provoke, perpetuate or permanently exaggerate chronic hypertensive disease, antecedent hypertension no longer is a blanket indication for therapeutic abortion. Furthermore, the threat to the life of the mother with antecedent hypertension who is properly managed during pregnancy has likewise virtually disappeared. On the other hand, if the underlying hypertension has progressed to the point where cardiac or renal failure is clinically recognizable, this provides an adequate basis for therapeutic abortion. Certainly an antecedent cerebrovascular accident or funduscopic change beyond stage 2, including hemorrhages, exudates and marked arteriolar spasm, provides unquestioned grounds for performing a therapeutic abortion. The more difficult group is that in which definite involvement of the heart, as reflected in fluoroscopic or electrocardiographic changes, has occurred without evidence of other organ involvement. In this group, unless unusually favorable conditions for careful management exist, therapeutic abortion is probably also indicated. A similar conclusion may apply to patients with renal involvement as indicated by persistent albuminuria without detectable evidence of reduced renal function. Certainly antecedent hypertension without evidence of organ involvement does not serve as a general basis for therapeutic abortion.

In patients with antecedent renal disease, any reduction in renal function is adequate indication for therapeutic abortion. The presence of a nephrotic syndrome, regardless of specific etiology, is a similar indication. A single kidney, if previously damaged or hydronephrotic, similarly provides indication for therapeutic abortion. Disseminated lupus erythematosus with distinct renal involvement, regardless of the precise level of renal function, should call for pregnancy termination. However, albuminuria secondary to latent chronic glomerulonephritis with normal renal function, a past history of acute diffuse glomerulonephritis with complete clinical recovery, previous pyelonephritis with normal renal function, or polycystic kidneys, with well preserved kidney function, do not serve as indications for therapeutic abortion. Previous nephrolithiasis when due to hyperparathyroidism, cystinuria, or oxalosis, may demand intervention.

Indications for sterilization in the nonpregnant or puerperal state may be less rigid than those held in regard to therapeutic abortion. This obviously applies equally to hypertensive and renal problems as well as other medical conditions.

## SUMMARY

Preeclampsia-eclampsia is a disease of unknown cause, which is present only in the pregnant human female, and which when fully developed cannot be cured except by evacuation of the uterus. The maternal organism can be protected by reducing the severity of the manifestations of the disease and to a lesser extent, its incidence. This malady is one of the main reasons for prenatal care. The disease has greater risk for the maternal organism if there is pre-existing cardiovascular-renal disability. Efforts to reduce perinatal mortality have been less successful because of vascular placental failure which has no specific treatment.

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With his passing, Mount Sinai has lost a distinguished alumnus, his colleagues and pupils an inspiration and a guide, and his countless patients a dedicated physician whose scientific knowledge was paralleled only by his unique richness of human understanding. His many friends, in turn, have lost a gracious companion, a mentor of integrity and an example of endless altruism.

Dr. Volterra, the son of a distinguished physician, was born in Florence on the second of June in 1901. At the age of twenty-three he received a Cum Laude Medical Degree from the University of Florence. After his graduation, he joined Professor Chiarugi's department as an Assistant in Anatomy. From this period come his observations on the reticulum endothelial system, which provided the groundwork for later studies in this area of investigation.

In the summer of 1925, he attended Professor Volhard's Clinic at Halle University in Germany. On his return to Florence, he received the appointment of Assistant in Medicine in Professor Schupfer's department, at the University. His next ten years at the Atheneum are an example of dedication to teaching and research.

In 1935, he was given the Chair of Medicine at the University of Cagliari, on the island of Sardinia. In the following year he was called back to his native Florence to teach Physical Diagnosis at the University.

Dr. Volterra made his most important contributions in the field of the blood dyscrasias. However, his interest in the medical sciences was so broad and universal that he never hesitated to overstep the boundaries of his immediate discipline.

In 1928 he made an important study on the epidemiology of Psittacosis. The same year he worked with Professor Kolle in the Institute of Experimental Therapy in Frankfort, and then with Professor Umber in Berlin in the Department of Internal Medicine. In the summer of 1930 he returned to Frankfort at the request of Professor Kolle, in order to pursue original investigations in basic oncology. In the fall of 1931, he was engaged with Professor Rein of Friebourg in studies on the circulatory system.

In December 1938, as racial prejudice shook the foundations of human rights, he emigrated to Switzerland. He stayed briefly in Professor Askanazy's department, and brought to a conclusion his classical study on the aromatic substances of the blood.



DR. MARIO VOLTERRA  
1901-1960

On the invitation of Dr. Rosenthal, he came to the United States in May of 1939 to join the staff of the Department of Hematology at The Mount Sinai Hospital. In 1945 he was appointed Senior Clinical Assistant in the same department, and in 1947 he was promoted to the position of Physician Adjunct.

In Mount Sinai Dr. Volterra found his new home. And in Dr. Volterra, Mount Sinai found a scientist and humanist worthy of the Hospital's tradition.

During his stay in the United States, the gracious teacher continued to give, generously and liberally. He participated in postgraduate courses of instruction given at the Academy of Medicine in New York, Columbia University, and the Ecole des Hautes Etudes, a branch of the Sorbonne of Paris operating in New York during the German occupation of France.

As peace was returned to the world, Dr. Volterra returned to Italy. He assisted the Italian government in the establishment of blood banks throughout the country, and he was instrumental in creating the Italian association of blood banks. He also represented the Italian government in the World Health Organization. In 1953, he returned to his native city as Chief of the Medical Service of Santa Maria Nuova Hospital and Director of the Medical Division of the Hospital of Careggi, positions that he held to the end.

Dr. Volterra has left to us more than eighty publications. Undoubtedly there would have been many more, but his great generosity made him take more personal pride in the accomplishments of his pupils than in his own achievements.

To his dear wife Bianca Levi Volterra, whose strength and devotion supported him throughout his endeavors, and to his daughters, Anna and Sara, who gave to his life so much joy and happiness, all of us extend our most heart-felt sympathy.

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# THE NATURE OF ANIMAL COMMUNICATION AND ITS RELATION TO LANGUAGE IN MAN\*

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"Man has great power of speech, but the greater part thereof is empty and deceitful. The animals have little, but that little is useful and true; and better is a small and certain thing than a great falsehood".

Leonardo da Vinci.

Speech is a human prerogative but to make this assertion is not to deny that "purposeful" communication may take place in certain subhominid species. In order to confine my remarks within reasonable bounds I propose to omit any mention of the insect noises produced by various processes of stridulation, and also of the sounds emanating from fishes, crustacea, amphibians and reptiles. Neither shall I refer to the global pantomimic activities of bees and other insects. Instead, I am proposing to dwell upon vocalisation within the animal kingdom, that is to say the sounds emitted by way of an anatomical specialization within the respiratory system of a bellows-and-reed kind. Consequently, I shall be confining my remarks to communicative behaviour among birds and mammals. As the argument proceeds, however, it will be found that the communicative activity within these species is not necessarily restricted to a system of vocalisation, for it is often complex, and may transcend the purely acoustic sphere.

Bird-sounds may be discussed as forming an important introduction to the subject of animal communication. Their audible repertoire is elaborate, for birds are essentially vocal creatures compared with other vertebrates.

"But birds vary as to the diversity of their song. Song proceeds from small birds rather than large; males and not females; arboreal as opposed to coastal dwellers; and birds of sober hue rather than those with bright-coloured plumage. Birds sing in the mornings and evenings, but not at noontide; and in fine weather rather than inclement weather" (Witchell).

Bird-song may be regarded as learned or imitative, while calls and cries are innate and instinctive. Song is not the only example of mimicry among birds, which often reproduce other sounds in nature including those peculiar to birds of different species, as well as mammals and even humans. Here belong the "talking" abilities of parrots, magpies, jackdaws, mynahs, and kuckaburras, phenomena which cannot be strictly regarded as communicative. Parrots may utter articulate speech in a convincing fashion, but under natural conditions they emit only a few shrill cacophonous screeches.

We may even discern a phenomenon of regional dialect occurring in birds of

The Israel Wechsler Lecture 1960, of The Mount Sinai Hospital, New York, N. Y.

\* Some of this material already formed part of the author's Hunterian Oration for 1958, which was later published in the Transactions of the Hunterian Society (London) for 1958-59. The text has however been drastically revised and additional subject-matter incorporated.

the same species but inhabiting widely separated districts: these qualities of accent are transmitted by a process of unconscious contagion, just as in humans.

Many writers have stated that if it is legitimate to speak of "language" of birds, it is their calls (rather than their song) which merit this appellation. Nevertheless, field ornithology shows that an elaborate and coordinated combination of song with motor activity, serves something more than an autistic function. Witness the various types of "display" which birds perform during certain important sociophysiological activities, *e.g.*, courtship, feeding, territorial pretension, nesting and migration. Some of these displays are communicative in effect if not indeed in intention. Two examples may be quoted. Thus, during its so-called gaping display, a bird of paradise starts by giving voice to several notes and squeaks; then it spreads out its wings and every now and again hides its head. Then stretching upright as far as possible, it flaps its wings as though about to take flight. Giving a half-turn, it now puffs out its silky-white underfeathers, and proceeds to emit a melodious warbling song (Ingram). In the "half-trumpet" display, a penguin utters throaty growls with the head and body leaning forward and the flippers hanging limply. Then follows the "full-trumpet" where the voice becomes louder. The penguin now stands erect and rhythmically beats its flippers in time with its song. Finally the bird throws its head right back with its beak pointing directly upwards, while the noise increases loudly in volume. Afterwards the flippers are pressed tightly against the torso (Richdale, Warham, *et al*).

Some bird-displays are self-evident in character, but others are difficult for an observer to comprehend, for they may resemble an elaborate esoteric ceremonial. Some are of a type which might even be deemed quite inappropriate to the situation. Thus, excitement, fear, or pain may provoke a bird to burst into song: a lark which has escaped from the clutches of a hawk may trill loudly. Naturalists regard these phenomena as being the expression of a side-tracking of energy, and speak of "substitute" or "displacement" activity. Particularly impressive to a student of language are the reciprocal pantomimic and vocal activities carried out by a pair of birds, like the performers of a well-rehearsed song and dance. Gillespie has written "I have seen two birds standing only a few feet from one another, trumpeting to each other in this way, and the whole affair had a delicious air of formality and correctness, each penguin being careful never to interrupt the other, but to allow his partner in the duet full time to complete his final note and fully relax before replying".

I want to emphasize this alliance of pantomimic display with vocalization. This has an important bearing upon such questions as the nature of bird-communication, and also the possible origin of human language out of gesture. Although most writers when discussing the problem of song, have tended to neglect the concomitant postures and movements, it is wrong to do so and to ignore the complicated pantomimic ceremonial so characteristic of bird-life. Bird-display does not appeal merely to a single special sense. It constitutes an art-form in which shape, colour, movement and sound combine to stir the spectator. At once there comes to mind an analogy with the ballet, and especially the stylized

systems of oriental dancing. In the same way it would be wrong to make too sharp a distinction between bird-song, bird-calls, and bird-cries. The apparent communicative properties of all these phenomena, vocal as well as motor, led Lorenz to describe them as "directors" or "releasers", though Tinbergen preferred the simpler term "signal".

Among mammals the anatomy of the sound-producing mechanisms shows an abrupt change from the conformation in birds and takes on a more human pattern. Between one mammalian species and another there are great differences in volubility though most of them lack the dramatic qualities of bird-song.

Correlation with the level of "intelligence"—whatever this word may mean—is not close, for some species are comparatively silent; some indeed are mute, even though they rank comparatively high as regards sagacity. Sound-range must be distinguished from sheer noisiness, for in some animals vocalization though loud and clamant, may be little more than an iteration of one or two sounds. Within a single species the repertoire of sounds may vary according to whether the animal is living in the wild state, captivity or domestication.

The primates, by and large, may be looked upon as noisy animals especially in their natural habitat, and they supplement their numerous cries with boisterous din-making. Some observers have been so impressed with the vocal attainments of primates that they have been tempted to read into their sounds both specificity and meaning. Vocabularies of monkey-speech have been prepared and transcribed phonetically in such a plausible fashion as almost to suggest the existence of actual primate dialects (which we might dub "gorillie" "chimpanzee" "baboonese" and orangutani"). But these enthusiastic descriptions are not scientific. Some writers, like Yerkes and Learned, are more cautious, and merely isolate "food-sounds" and "social-sounds". Although Yerkes and Yerkes have heard chimpanzees whine, moan, groan, grunt, bark, shout, yell, hoot, and scream, never have they felt sure that the term "speech" could fittingly be applied to these utterances. In their opinion none of the anthropoids can be said to "speak". Among apes, mutual understanding and transfer of experience depend upon sight rather than hearing, for one animal reads the mind of its fellow, interprets attitude, and foresees action more like a deaf-mute than a normal person relying upon linguistic clues.

These last points are particularly important. As in the case of birds, vocalization is associated with an abundant play of pantomimic movements. Intercommunication is probably effected by the "understanding" or reception not of individual or isolated sounds, but of a behavioural complex, wherein movement and sound are combined. The ape, in other words, appears to interpret the total situation as enacted by its companion. This belief tallies with the experience of primate-training. It is easier to teach an anthropoid to copy bodily attitudes and gestures, than to imitate sounds.

It is often said that nothing but cerebral incapacity prevents the higher primates from learning an articulate language, the peripheral equipment standing by, ready for mental maturity to be achieved. Recent comparative anatomical studies of the larynx have thrown some doubt upon that idea however. Kelemen

has shown that man-like vocalization is not possible in apes, for they are not structurally equipped. The differences between the larynges of man and the primates are all-important, and comprise a two-fold process of both increasing elaboration and increasing simplification.

Among primates the gorillas are unusual in the way they also produce sounds by nonvocal methods, like pounding of the thorax with the fists, rattling their teeth, beating their cheeks, stamping, and striking objects. These forms of din-making connote emotional excitement, or perhaps merely high spirits.

Let us pass from these purely observational accounts of animal noises to the more fundamental problems of their underlying meaning and their functional role. In this connection two seemingly opposite expressions of opinion may be quoted. Thus, Kroeber's contention that "animals do not talk, because they have nothing to say" may be contrasted with the opinion of Yerkes and Yerkes about the great apes. "These creatures" they wrote, "have plenty to talk about, but no gift for the use of sounds to represent individual as contrasted with racial, feelings or ideas".

How far can these two opinions be reconciled? Differences between the communicative systems of *homo sapiens* and the subhominids could be looked upon as matters of fundamental quality, or merely a question of degree. The former view, which implies a specificity of the human organism, has been argued by two very different schools of philosophy. On the one hand, there are the determinist views of the dialectical materialists who distinguish man from animals by the possession of a second, as opposed to a single system of signals, comprising "signals of signals". At the other extreme of philosophic thought also implying a qualitative difference, stand the theists who look upon man as a special creation, who alone is endowed with a soul and with the faculty of speech. Max Müller was the most eloquent champion of this idea. But in the other camp there is ranged a weight of biological opinion, even though few today would associate themselves with Garner, who argued that monkeys are endowed with a vocal system which discharges all the functions of speech. His views may be looked upon as an extreme example of anthropomorphic interpretation of animal behaviour. To attach a plausible and obvious explanation to a complicated piece of behaviour on the part of a bird or mammal, is only too seductive and the temptation should always be offset by applying the "canon of the minimum antecedent". Lloyd Morgan emphasized that an animal's activity should never be interpreted in terms of higher psychological processes, if it can be fairly explained by processes which are lower in the scale of psychological evolution and development. In other words we must always seek the "minimum" explanation of animal behaviour. This canon should also be applied to any too humanistic interpretation of sounds emitted by animals.

Is it then justifiable to assert that animals "speak" and that there exist in nature veritable systems of animal "speech"? The answer obviously turns upon what is understood by the term "speech". Many definitions are available, all possessing as a common and quintessential item the use of "articulate sound-signs" or "articulate words" as vehicles of information. Speech, be it noted, must be



articulate and comprise "words", capable of being recorded through the medium of graphic symbols. A system combining phonemes and morphemes is demanded.

But animal-sounds rarely, if ever, lend themselves to accurate phonetic transcription, and attempts to do so are but approximatic which indicate rather than reproduce the sounds in nature. Consequently they are not *sensu strictu*, articulate. Even more important is the objection that words are tools of thought which can be made to stand for an idea, abstract as well as concrete, and be consistent in this usage, the same word or morpheme being employed to relate to the same notion unhampered by variations in time and in space. No animal can do this.

On these counts, to be considered more fully later, the term "animal speech" must be considered unjustified.

Can one then refer with propriety to an "animal language", in contrast to "animal speech"? It becomes apparent that definitions of language which concentrate merely on the traffic in articulate sounds, are really definitions of speech, and do not include the role of language in other contexts. Although many American linguists restrict the term language to spoken speech, this is not and has not been a universal practice. Thus one commonly talks of the language of the dance, of gesture, of painting, of mathematics, and even of flowers: are we correct in so doing? All these notions entail the idea of language as a system of symbols. Though not a modern one, we may quote Thomson's definition of language as a "mode of expressing our thoughts by means of motions of the body; it would thus include spoken words, cries, involuntary gestures that indicate the feelings, even painting and sculpture, together with those contrivances which replace speech in situations where it cannot be employed". If we can agree to adopt such a broad conception of language, with its inclusion of "cries and involuntary gestures", then it would be justifiable to embrace the animal kingdom and to speak of an "animal language". But most linguists lay more emphasis upon the role of symbols (spoken, written, mimed, painted or hewn) as being the *sine qua non* of language, the term "symbol" meaning an arbitrary sound or mark, used deliberately, and precisely, indicating something more than "signs" or "signals". Thus if we follow Head in speaking about "symbolic formulation and expression" it would be difficult to use the term "animal language" except perhaps in very narrow and quite exceptional circumstances. The problem shifts to the question of how far animals can utilize and manipulate symbols. On the whole, animals cannot be said to move in a climate of symbols, although again there may be times when this statement does not altogether apply, and when symbols of a vague kind come into operation. We may mention that some linguists now tend to avoid referring to "symbols" even though this term has been sanctioned by psychology and philosophy, and indeed has featured conspicuously in many classical linguistic texts.

To justify the use of the term "language", Bierens de Haan demanded six characteristics. He required the sounds to be vocal; to be articulate; to possess conventional meaning; to be indicative; and also intentional. Finally the sounds should continually be joined in varying combinations, so as to constitute phrases of differing content. Applying these criteria to the audible communication in

animals, the author asserted that most species are dumb, or that the sounds they emit are not produced orally. Those animals which are vocal are articulate only exceptionally. Animal sounds are devoid of conventional meaning, in that they express sentiments rather than situations or objects. Sounds in the animal world are not produced with the purpose of expressing something, even though secondarily and unintentionally they may serve as a means of communication. Animals cannot emulate man in creating new words or new phrases out of a stock of existing words. "Language" is therefore a term which cannot be applied to animals. Nor can the natural sound-systems of animals ever attain the status of a language under the influence of man or in the circumstances of training.

Hockett has lately identified 13 separate properties or characters of language under the term "design-features". Many of these are also to be traced in some of the animal communicative systems; others appear to be peculiar to man. The latter comprise what Hockett has called (1) displacement; (2) productivity; and (3) duality. These expressions obviously need to be interpreted. "Displacement" is of course Pumphrey's "extensibility", and indicates the ability while communicating, to transcend the barriers of immediacy in time and place. With the possible exception of the dancing system of communication among bees, this property is rare outside of human behaviour. "Productivity" is the factor whereby in language new messages may be coined, and then intelligently received or decoded. This property is bound up with the availability of morphemes, which serve as elementary signalling units. Hence, there obtains an "open" semantic system which can even permit the encoding of information which is false. "Duality of patterning" refers to the basic structure of language into morphemes made up out of phonemes. This would appear to be a human characteristic, even though Hockett has cogitated whether "significant duality" as he calls it may not perhaps also be encountered in the complex song-systems of some passerine birds. Cultural transmission, or more simply "tradition", is another of Hockett's design-features, but it may not perhaps be altogether a perquisite of *homo sapiens* although it materially assists the development of an organised system of communication.

Obviously we would be on insecure grounds if we were to talk about the existence of "animal language", and it would appear safer and wiser to avoid such a term altogether. Similarly, the terms "pseudo-language" and "rudi-language" proposed by Boutan and by Wilson should be discarded.

Since animal "speech" and animal "language" are objectionable terms, would not "animal communication" prove acceptable? Nowadays the communicative character of language is being emphasized more and more, and the word "communication" certainly avoids the inference that verbalization is the sole medium. The use of this term naturally raises the question as to the nature of animal vocalization and display, and whether indeed these can logically be regarded as essentially communicative in every circumstance or context.

Révész regarded the sounds emitted by animals as falling into three main categories, *viz.* (1) self-expression; (2) wordless cries; and (3) directed calls. The purring of a contented cat and the trilling of a solitary caged bird exemplify

the first of these, and can scarcely be rated high in the scale of communication. The other two, however, can be looked upon as potentially communicative. Although this classification does not altogether satisfy, it goes some way towards clarifying the nature of the problem, the cry—the adjective “wordless” is distracting and unnecessary—is instinctive; nonarticulated; unconcentrated and vague; it is “directed”, but not towards any definite individual. It is an attempt to induce the external world to cooperate in some fitting way. The communicative tendency is expressed by the fact that the animal seemingly senses the proximity of a creature that can free it from its state of unease. Lloyd Morgan regarded the primary purpose of animal sounds as serving to indicate a comforting presence; and he spoke of “. . . the reassuring social links of sound, the grateful signs of kindred presence”. Cries may also be produced without deliberate communicative intent, but they have a communicative effect none the less. A frightened animal does not necessarily emit a cry with the object of warning its fellows; the cry merely instinctively expresses the animal's own fear, which automatically produces fear in the others within audible range. De Laguna adopted a different nomenclature. She equated animal cries with the function of proclamation. She isolated four types though admitting that they tended to merge. Her classification was as follows:—(1) Proclamation of presence; (2) Predicative proclamation; (3) The announcement of intention; and (4) The announcement of accomplishment.

The directed call (or better still, the “call”) differs from the cry in that it possesses individual reference. The call is explicitly addressed to someone. The sensible presence of a partner is required. Furthermore, the call possesses an imperative character. Unlike the cry (which is instinctive by nature) the call is bound up with individual experience. Place-reference constitutes yet another characteristic of the call, as opposed to the cry, for the animal indicates the place, object and person addressed. Finally there is a vocative component to the call which does not apply to the cry.

It may be objected that the antinomy of “cries” and “calls” does not really include that very individual expression of animal-behaviour, namely bird-song. A reluctance to define “song” is very obvious in the literature of ornithology.

Between the communicative type of vocalization and that which seems to be purely autistic, egocentric, intransitive, ludic, *i.e.*, non-communicative, there exists an intermediate group. This is what Griffin has called “echo-ranging”, “echo-locational”, or “sonar”, and consists in a sort of solipsistic “language” or “talking”—not to others of the same species, nor to itself, but to its own environment. Orientation-sounds are emitted by the animal and information is obtained from their echoes. No second animal is involved. Echo-location, according to Griffin, is employed to convey precise and subtle information back to the animal from various objects in the surrounding world. This kind of communication is best illustrated by bats which possess an extraordinary sensitivity and discrimination in the use of this particular acoustic tool, in orientating themselves in the dark, and in catching insects on the wing. Also porpoises and dolphins probably navigate themselves in the dark and in turbid water by a supersonic

system of echo-location, and they can avoid obstacles and locate foodstuff with uncanny accuracy and speed.

Communication is but one aspect of animal behaviour. As such, it raises the interesting Ausloeser conception put forward by Lorenz, elaborated by Tinbergen, and studied particularly in birds and other sub-mammalians. According to these authors, animals show innate behavioural responses to certain specific attributes within their environment, whether these be in the nature of significant shapes, colours, attitudes, movements, sounds, or scents, singly or combined. In that these attributes determine a response upon the creature's part, they are termed *Auslöser* or "releasers". The reaction is believed to depend upon a special central nervous mechanism called the "innate releasing mechanism". It is clear that only certain environmental attributes act as releasers. Russell has spoken of these influential stimuli as "perceptual signs" or as "perceptual clues", though Tinbergen preferred the term "sign stimuli". In that certain bodily postures and miming with or without audible vocalization, may serve as releasers, they can be looked upon as a modality of communication entailing an actor and a reactor. When such a realiser evokes a response which itself is a movement-sound complex, the role of communication becomes still more evident.

Tinbergen (1951), has also introduced the notion of the "inserted link" which lies between perception and the ultimate adoption response,—and forms a sort of signal-system. The author intimated that even human language might be capable of discussion along the lines of an "inserted link". As Tinbergen has put it "... movements effect organs, innate releasing mechanisms are fitted together; they act as a wonderful, complicated system the only function of which is the construction of a means of social communication. In fact, such complicated structures are understandable—they "make sense"—only in connection with their function; the coincident presence in the same species of stridulation organs, the stridulation drive, and an innate tendency to react in certain "purposive" ways can be recognised as an adaptive feature only when the releaser function is recognised".

Reflection upon these topics raises the suspicion that no sharp demarcation exists, or can be attempted, between all these vocal phenomena in nature. Between cries, song, calls, simple expressive sounds, and the effect of releasers, the gradations are so tenuous that classification is difficult indeed. Obviously there is a need for a more logical terminology. A simple all-embracing term is required to include all the sounds emanating from the respiratory apparatus which are evoked in the animal kingdom. "Psophic communication" has been suggested, but "vocalization" is perhaps the least objectionable term.

According to modern information-theory, all communicative acts entail a sender, a receiver and a message. We have seen that in the case of animals, the aspect of "message" may at times be inconsiderable. Very often it would seem that the animal or bird gives voice without any clear "purpose" unless it would be to derive some satisfaction or enjoyment thereby. One cannot trace any specific difference here between the behaviour of animals and humans, for children and even adults not infrequently speak merely for "ludic" or egocentric



purposes. The receptive side of animal communication is also of different character from that in humans. As E. S. Russell has emphasized, an animal possesses its own private perceptual world—its *Umwelt*, as von Uexkuell called it. This explains a creature's apparent indifference to so much of its environment stimuli, auditory as well as visual. At the same time animals may be uncannily responsive to quite minute events in the environment, changes which may elude our less sensitive perceptions, but which nevertheless possess abundant valence for the animal. These subtle clues, as a matter of fact, are more often optical than auditory.

Nevertheless, to equate animal sounds with communication would not be to fall into serious error. True, the communicative action may not always be intentional, as far as we can discern. The cry uttered by a startled bird can be best regarded as an instinctive expression of fear which happens to provoke a kindred emotion among others of its species within earshot. But the original cry may not really have been a deliberate message to the others, even though it actually resulted in instinctive reaction on their part. We can say that the cry was therefore communicative in effect, though not in purpose.

Much of animal vocalization is to be looked upon as the expression of the upsurge of powerful emotion. This audible reaction may relieve tension in the animal itself. It may also interest, excite, or even influence the behaviour of other animals, but this effect (however desirable it be from a teleological standpoint) lies outside any process of volition or will.

The points of distinction between animal vocalization and man's articulate speech may now be discussed.

According to Pumphrey three factors are peculiar to human speech, namely (1) detachment; (2) extensibility; and (3) economy. By these terms the author meant that in the first place man, unlike animals, is able to use verbal symbols in a wholly dispassionate fashion should he so wish. Extensibility is another way of saying that a proposition can be made or discussed in terms of present, past or future time. The factor of economy stresses the value of symbols in enabling man to condense what might otherwise be a lengthy reiteration of descriptive signs.

The verbal symbols which make up the structure of human speech are, in essence, arbitrary and conventional. Consequently, they are mutable to an almost unlimited degree and can increase or change *pari passu* with maturation of ideas. The symbols are not self-evident in purport; they are conventional and need to be learned. In contrast the vocalization of animals is not made up of symbols. Animal sounds are essentially natural, innate, instinctive, and spontaneous, even though mimicry may mask the picture. The sounds do not vary from one generation to another; in each individual member of a species they rest intact and self-sufficient.

The principal difference may therefore be summarized by stating that while an animal's sounds entail signs, man's speech is made up of symbols. Signs indicate things, while symbols *represent* them. Signs may be looked upon as announcers of events, and symbols as reminders. Symbols are "substitute" signs, for they can take the place of things out of sight and not in present experience.

To jettison the term "symbol" as some would have us do, because it is a complex or even clumsy connotation, capable of analysis into component particles, is not, I submit, justifiable. The very latitude of the term is in many circumstances an advantage.

Man's use of verbal symbols can be regarded not only as a product of his superior mentation but also as a reciprocal influence which augments, deepens, and enriches his power of thought.

An ape makes a noise when hungry; this might be interpreted by us a declaration; or an imperative utterance; or merely an exclamation betraying discomfort. But no ape has ever uttered the word "banana", for such a word is a morpheme, a concrete symbol, a tool of thought which man alone can employ; and in a variety of ways, irrespective of time and space. Man can refer to a banana in the past or future tense, as well as the present. Man can talk about a banana not only when it lies under his nose, but also *in absentia*. No animal can do this: the task is far beyond its capacity of thought and therefore of sounds. Furthermore, no monkey can utter the word "hunger", for this is an abstraction, a universal, a "general idea". In other words no animal possesses the "time-binding" faculty which is essentially a prerogative of man and which has determined his dramatic progress.

Many animal vocalizations are characterized by a repetitive quality, the creature emitting the same sound from its scanty repertoire over and over again. A dog with its incessant bark; a lion roaring throughout the night; a solitary canary warbling in its cage, are all cases in point. Often it is difficult to detect any "meaning" or purpose to these sounds, which do not appear to be cries of emotional origin, nor yet communicative calls. Possibly some of them represent yet another instance of play, but one must not be anthropocentric. Most of them remain quite obscure and beyond our present powers of interpretation. As Schwidetzky has said, "it is simpler to translate thirty pages of Cicero than to define the meaning of a crocodile's grunt".

In the case of man, however, speech may be a wholly independent form of behaviour. The words spoken need not occur merely as an element in a larger response. This fact illustrates Pumphrey's quality of detachment which scarcely ever applies to animal noises. Similarly, human speech may be wholly devoid of any emotional content: this is not so with animals, where cries are the true mirror of the feelings of the moment. The differences go even deeper. A man may speak with the express intention of masking his feelings; or concealing thought; or deceiving the listener. Nothing like this occurs in the animal world unless we include certain audible displacement-activities. Nay more; man in his communication may deliberately employ the device of *silence* as a dramatic method of expressing feelings or ideas. Such a phenomenon does not occur in the animal world, other than the sudden hush which comes over a community in circumstances of immediate danger.

Another distinction between animal and human communication derives from the intimate linkage of animal cry with immediate emotional tension. The animal's cry or call, cannot do more than proclaim a situation (*e.g.* danger, food) whereas speech can specify the situation and describe it.

The superiority of speech over animal cries as a means of social control is obvious. Cooperative behaviour among animals is instinctive; while in man, thanks to the endowment of speech, it is "intelligent". A system of animal cries would not suffice to cope with novel modes of cooperative activity. Human speech evolved along with an increasingly elaborate communal life. The making and transport of tools; planned hunting forays; the need to secure safety at night; the indoctrination of the young by experienced elders; these are some of the activities of early *homo sapiens* which must have been materially assisted by the power of speech. Expressed differently, we can recognise that an important survival-value stems from the possession of speech.

Another difference between the vocalization of animals and speech is one which derives from neurology. I refer to the vulnerability of human speech to states of disease or injury. This property of language was noted by Aristotle even though few subsequent philosophers and biologists have referred to it. Aristotle asserted that man alone is apt to display dumbness or hesitancy in speech, implying a failure to explain one's meaning adequately. It is true that nothing comparable with an aphasia in the strict sense of the word occurs in animals even after extensive ablations of the cerebral cortex.

A fundamental question concerns the nature of the mechanisms whereby the most elaborate types of animal communication merge into the speech of *homo sapiens*. One uses the word "merge" because the belief in a sudden appearance of some quite novel acquisition is, rightly or wrongly, out of scientific favor today. An all-important role in this transition is believed to be played by a marked elaboration of the social organization of early man. This was the basis of Révész's "contact theory" of the origins of speech in man. However the biological axiom must not be overlooked, namely that group-existence is characteristic of all animal life, from the lowest to the highest. But with the appearance of *homo sapiens* a number of elaborations occur in which linguistic development plays a vital role. What are the social features which characterize human communal life? Some believe that division of labour is all-important. Others would point to the phenomenon whereby individual members behave differently in the presence of others from their comportment when alone.

The first manufacture of tools marks a critical point in evolution, and *homo sapiens* is at one and the same time, *homo faber* and *homo loquens*. Both language and tools are instruments which humans alone employ to achieve definite and tangible aims. "Moreover, language, like the tool, and unlike the limb, is something objective to, and independent of, the individual who uses it. It is a factor which he finds in his psychological environment, and to which he must adapt himself. It has a structure of its own which he must learn to take account of in his use of it" (de Laguna). Even more significant than the use of tools and of language is the fact that man alone can devise, construct and elaborate them. To this property must be added the *carrying* of tools, though this may lie between the use and the fashioning of tools.

Hockett has laid emphasis upon the possible role of what he called "blending" during these crucial steps of transition. Two words may be accidentally confused

so as to produce a neologism which contains parts of the two words in question—a familiar enough phenomenon to aphasiologists. It has been suggested that eventually one of these neologisms “catches on” and becomes accepted within the corpus of a communicative system as a useful addition.

Clearly the transition from animal vocalisation to speech is not entirely a problem of linguistics. We believe with Sapir and Suzanne Langer, that the origin of language is really part of a larger question which ties up with the beginning of symbolic behaviour in animals. Langer has suggested that the earliest sign of this trend is an apparent sense of significance which an animal may attach to certain objects, forms or sounds. In the behaviour of the anthropoids, one can at times detect clues that some objects—quite limited in number and in occurrence—may seem to possess for them a “meaning”; to convey something; to be significant; to be valent. How often chimpanzees in captivity utilize inanimate objects as playthings—sticks, pebbles, shreds of rag. Here then we discern the dawn of symbolic thought; and here perhaps we may desery the remote ancestry of speech. In other words, the chimpanzee, although devoid of speech, begins to show a rudimentary capacity for speech. Conceptually, he is not far off its attainment, an opinion which reminds us of Max Müller’s uneasy feeling that the gorilla is “behind us; close on our heels”.

Discussion upon animal communication naturally involves an enquiry into the nature of animal thinking. Apart from experimental studies of animal sagacity, maze-learning, and conditioned responses, but little is known about the nature of an animal’s mental rumination. During its waking but inactive moments, an animal obviously does not utilize an imagery made up of verbal symbols. But an imaginal type of thinking probably exists and may well take the form of perceptual complexes of a vague character. Abstractions are largely beyond the capacity of an animal, though it may be trained to utilize or act upon abstractions. When Thorndike said that animals “think things, but do not think about things”, he was indicating the concrete nature of their imagery.

The limitations of animal intelligence and powers of communication make it difficult for us to conceive of them planning or thinking ahead except in rare and special circumstances. Of course animals sometimes anticipate events, as in the rituals of nest-building, migration or prehibernation activity, but these are almost certainly instinctive proleptic drives, and not premeditated acts. Without words an animal cannot achieve much in the way of complicated planning, as in the corporate action of man. An animal’s inability to employ spatial and temporal orientations in its mental processes is reflected in the poverty of its vocal utterances. Man’s power of explicit mental differentiation brought language into being, as R. A. Wilson said.

To what extent do animals, particularly those in domestication “comprehend” the speech of man? Exaggerated claims are made at times, but it is doubtful how far they can be scientifically sustained. Samuel Butler must not be taken too seriously when he wrote: “It is idle to say that a cat does not know what the cat’s-meat man means when he says “meat”. The cat knows just as well, neither better nor worse than the cat’s-meat man does, and a great deal better



than I myself understand much that is said by some very clever people at Oxford or Cambridge." As a matter of fact, a cat associates the presence of a cat's-meat man with food by dint of a veritable medley of clues, olfactory, situational, gestural. The sound of the word "meat"—should it come into the picture at all—is a mere signal, comparable with a flashing light, or a bell in the case of a laboratory animal. There has recently been an amusing correspondence in the British Press about the regional differences in the noises commonly employed to attract the attention of the domestic cat. Whereas "Puss Puss" is commonplace for most of England, there are areas where some such call as "ch eh" is preferred. Dr. Samuel Johnson's alleged remarks upon this topic were recalled: *Boswell*: "Is it not strange that the mode of address to a cat varies with its geographical habitat?" *Johnson*: "A cat will respond to any familiar fulmination which it knows from experience is a promissory of a reward". *Boswell*: "But is it not strange that in some districts we say "Puss" and in others "ch eh"? *Johnson*: "No sir, it is not so strange as the fact that an Englishman says "Yes", whereas a Frenchman, for reasons no philosopher comprehends, says "oui"." Those who fondly imagine that their domestic pets really identify and interpret the purport of items of human speech, often quote the evidence of Clever Hans the calculating horse, and the "talking-dogs" who spell and answer questions. The famous Elberfeld horses used to signal by hoof-taps the answer to arithmetical problems involving the four primary rules, fractions, brackets, the extraction and multiplication of roots, and the solution of equations. After thorough investigation it was concluded that this was an elaborate trick. Animals, especially when in domestication, are apt to display a sensitivity to a total situation which on the face of it gives the impression of an uncanny understanding of human speech. The truth is, that it is not so much the audible morpheme which is comprehended as the paralinguistic accompaniments of tone, pitch, loudness and rate of speaking. Still more significant are the nonverbal clues, made up of the gestures of the speaker, and of other environmental circumstances perhaps too subtle to attract our notice. As Lorenz has said, among social animals the apparatus of "mood-convection" is much better developed than it is with us, and so they become responsive to minute intention-displaying movements made by humans, and also by other animals. These calculating horses of Elberfeld were merely highly trained animals which responded to minimal clues on the part of the impressario, conscious or unconscious. None of the horses could solve a problem which was beyond the competency of the trainer.

An animal's apparent but often inconsistent recognition of human speech is merely a special instance of what has already been said about the nature of perception in animals. Some items of the visual and acoustic environment are simply ignored, for they possess no meaning for the animal, or better, no "valence". On the other hand, a complex of sense-data may prove valent or significant, such for example as the tone of voice combined with a gesture. These, placed against an appropriate background of events, may combine to form a stimulus which is far more valent than the mere phonemic structure of the words

of command. We must realize that animals in general do not perceive their surroundings in such an "articulated" way as we do. Their perceptual world is not a coordinated compound of clearly separate and distinct objects. Things are perceived only as ill-distinguished parts of a general complex, and always in relation to that complex, so that when a thing is isolated from its normal context it may not be recognized for what it is. Animals may react to perception-complexes comprising linkages of ill-differentiated objects. We must not assume that the features of a perceptual field which are significant to us, are necessarily those which appear significant to an animal. In the auditory sphere the same arguments hold true. A dog may act as if deaf to many sounds though they must surely reach its ear. The perception, however, is highly specific and the animal may react promptly to whichever noise possesses a definite valence, and to that alone.

Animals also vary considerably in their response to the sounds evoked by other animals, especially those of different species. Unless immediate danger threatens, animals are often singularly inattentive to the cries of other creatures; but here again inconsistencies occur. This may be exemplified by the effect of recorded animal noises upon pet animals when played over in their hearing. Dogs and cats sometimes appear quite uninterested; at other times they take notice; sometimes they even show excitement and frantically search for the intruder. Once again movement may prove a more efficient signalling system than sound. Thus the flight of the startled sentry birds away from their perch upon the back of a rhinoceros may serve as an adequate alarm to the host of the proximity of a dangerous situation.

At this juncture I would like to re-emphasize the alliance in animal communication of bodily movements with sounds. Insofar as an animal of one species comprehends the primitive message which may be emitted by another of its kind, the perception is an "interpretation" of or a "response to" a complex of activity, wherein sound forms only a part. Natural historians look upon this as a rule throughout the animal kingdom; it is conspicuous in the case of birds and primates, which incidentally are the most vocal of all creatures. Many biologists believe that in the chimpanzee vocalization is an even less important means of intercommunication than pantomime. In stressing this combined motor-vocal quality of animal communication, we cannot however agree with Wundt who visualized two distinct hierarchies of behaviour whereby oral speech arose, as a modification of general movements.

It is interesting to speculate which component of animal communication proved to be the most important step in the march towards language in man. Was it the gestural system, or the audible cries and calls? One can easily overlook the part played by the former, and assume that audible systems of communication were all-important. A gestural hypothesis as to the origin of speech was once held by many, even though few believed that there ever existed a *homo alalus*, representing a stage in prehistory when man gestured and did not speak. But throughout the vertebrate series, bodily movements have always been important, as in the rituals of display among birds. Mammals on the whole betray

their feelings by a different type of movement-complex, a conspicuous part being played by horripilation, baring of the fangs, lashing of the tail, arching of the back and so on. In the case of man these latter phenomena are represented by such autonomic signs as flushing or blanching; dilatation of the pupils; and sweating. These are largely beyond the control of volition. They are communicative in effect, whether or not in intention also, just as in the case of many animal cries. Man also possesses an eloquent language of gesture of a different kind.

Assuming arboreal habits the primate began to use the forelimbs for prehension as well as locomotion; man alone uses the forelimbs exclusively as tools. In man they may serve as adjuvants of speech. Mimic movements made with the arms and hands emphasize his utterance, and may even take the place of audible speech. This pantomime is a direct though remote descendant of the ritual displays in the bird-world. Furthermore, between these deliberate gestures and the involuntary autonomic phenomena, man utilizes, more or less automatically, a variety of facial movements which betray the feelings. Here belong tears, frowning, scowling, smiling, laughter, and many other grimaces. These may occur in silence; or they may accompany the sound-track of speech so as to give emphasis. Although automatic, they can be inhibited by a deliberate effort of will, so that what is spoken and mimed need not necessarily be the true index of thought, and opportunities arise for deceit (or negative information).

Among the many anatomical modifications culminating in *homo sapiens*, linguists will take note of the disappearance of hair from the dorsum of the body and from the face. This facial hairlessness reveals the play of the muscles of expression, a fact which might appeal to those who support the gestural origin of speech. The difference in the sexes as far as facial hirsutism is concerned must not be overlooked, and if we were unreservedly to accept the gestural hypothesis, we might be tempted to ascribe a more important role in the genesis and maturation of speech to primitive woman rather than to primitive man. And why not indeed? For there are many imposing linguistic arguments which could be marshalled to demonstrate the significant part women play in molding, elaborating, and even changing our language.

In conclusion, let us realize that there probably exist in the animal world systems of intercommunication of which we as yet know nothing. Among bees the language of the dance may be merely one of many other elaborate codes. We have referred to the supersonic methods of echo-location practised by bats, and by porpoises and whales. Some of these are not only exploratory but also communicative; transitive as well as intransitive. We must not imagine that all these obscure systems of animal-communication are essentially acoustic in nature. They may well be tactile, chemical, or olfactory.

May I now conclude my remarks upon this fundamental topic by quoting from the ornithologist Eliot Howard?—"... I seek the nature of a bird's world, not with any hope of finding it, but to know what to find. There is more joy in finding a problem than in trying to solve one, for to solve a problem is vain delusion. There is a mystery of flight; a mystery of song; a mystery of a nest; and yet, not three mysteries, but one: a bird is the mystery, for it steals our values of beauty and mingles them strangely in form no less than in feathers;

in colour no less than in song; and in what we value most, devotion to its home. And no less strangely it seems to mingle the blindness of an insect with the intelligence of an ape; and because nothing is really blind and no one is likely to know what intelligence really is, mysteries will be mysteries still. I would not change it. . . ."

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# HYPERCALCEMIA AND NEPHROCALCINOSIS IN SARCOIDOSIS

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The recognition of hypercalcemia in patients with sarcoidosis is not only a diagnostic aid, but is of even greater importance in relation to management. Persistently high concentrations of serum calcium are conducive to renal damage, calculus formation, and metastatic calcification (1). Anorexia, nausea, and vomiting are common complaints of patients with hypercalcemia (2), and with marked increases in serum calcium, it has been shown that progressive lethargy and coma may develop within a few days (3-5). Since appropriate dietary and steroid therapy can lower serum calcium and reverse functional renal changes, it is essential that this therapy be promptly instituted to prevent the progressive and severe manifestations of the hypercalcemic state.

The following case is illustrative of some of these manifestations of hypercalcemia, with particular reference to renal complications.

## CASE REPORT

A 23 year old white female bank teller was referred to The Mount Sinai Hospital for admission because of anemia of eight months duration. The patient had always been in excellent health until thirteen months prior to admission. She noted generalized weakness and a forty pound weight loss over the next five months despite a good appetite. Eleven months before admission she developed polydipsia, polyuria, and an erythematous papular pruritic rash on the lower extremities, which faded within five months.

She was admitted to another hospital at this time and the following laboratory data were obtained: urine 1+ albumin, sugar negative, hemoglobin 9.3 Gm%, hematocrit 27%, red blood cells 3.2 million per cu mm, white blood cells 3,600 per cu mm with a normal differential count, reticulocytes 1.4%. Blood urea nitrogen was 15 mg% and a fasting blood sugar was 90 mg%. Bone marrow aspiration revealed a normoblastic marrow. The patient received three blood transfusions. After discharge she received liver and iron injections without significant change in the anemia. No specific diagnosis was made.

Anorexia, nausea, and occasional vomiting developed seven months prior to admission and the patient took two to three bromo-seltzers daily during this period. Easy bruising without trauma was noted at this time and a mild systolic hypertension (150) was found four months preceding hospitalization. Two months before admission typical herpes zoster lasting two weeks developed along the right chest wall.

It was noted that the patient drank two to three quarts of milk daily for the past seven years, but she took no vitamins and specifically no vitamin D. In 1957 while applying for employment she was found to have a hemoglobin of 10.3 Gm % and a negative urinalysis.

Family history revealed that her mother and father and eleven siblings were all well and that there was no familial history of disease.

On physical examination the patient appeared pale and chronically ill. Blood pressure was 145/90 mm Hg, pulse 100 per min. and regular, respirations 16 per min. and temperature 99 F. The only pertinent findings were: small, firm, movable, axillary, and inguinal adenopathy; band keratitis; a few small ecchymotic areas on arms and legs; liver was palpable two inches below the right costal margin; spleen was palpable two inches below the left costal margin. The remainder of the physical examination was within normal limits.

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The urine had a specific gravity of 1.010, 3+ protein, 1+ sugar (glucose), rare white and red blood cells per high power field, and was negative for acetone. A Sulkowitch test was 3+ and there was no Benec Jones protein.

The hemoglobin was 7.0 Gm % with a hematocrit of 22% and a red blood cell count of 2.8 million per cu mm. Platelets were 144,000 per cu mm, reticulocytes 2.2%, and the white blood cell count was 2,800 per cu mm with a normal differential. A Coombs test and three lupus preparations were negative. Blood chemistries revealed a blood urea nitrogen of 64 mg %, a fasting blood sugar of 68 mg %, a calcium of 12.1 mg % and a phosphorus of 5.1 mg %. Plasma bicarbonate was 16.2 mEq/L, and plasma sodium, potassium, and chloride were normal. A serum creatinine was 4.8 mg %. The serum total proteins were 7.0 Gm % of which serum globulin was 2.8 Gm, serum albumin was 4.2 Gm. Serum uric acid, bilirubin, alkaline phosphatase, and electrophoresis were all normal. A glucose tolerance test revealed a typical diabetic curve. On a Bauer-Aub diet a 24 hour urine specimen contained 344 mg of calcium (normal in this hospital is less than 100 mg).

ECG on admission revealed sinus tachycardia and a normal QT interval. Chest x-ray was normal except for an azygous lobe and bilateral cervical ribs. A flat film of the abdomen showed splenic enlargement and bilateral renal papillary calcifications consistent with nephrocalcinosis.

A liver biopsy was reported as showing multiple epithelioid and giant cell tubercles with Schaumann bodies diagnostic of sarcoid. An inguinal lymph node was suggestive of sarcoid with multiple discrete epithelioid granulomata, giant cells and no caseation. A bone marrow biopsy demonstrated moderate fatty infiltration without granulomata.

The patient was given 40 mg of prednisone daily and at the time of discharge she was much improved with hemoglobin of 10.4 Gm %, platelet count of 158,000 per cu mm and a white blood cell count of 5,850 per cu mm with normal differential. A serum calcium was 10.1 mg %, serum phosphorus 3.4 mg %, blood urea nitrogen 46 mg % and the serum creatinine had fallen to 3.3 mg %.

#### DISCUSSION

In the differential diagnosis of hypercalcemia the following entities must be considered: hyperparathyroidism (6, 7); hyperthyroidism (8-10); multiple myeloma (11, 12); Hodgkin's disease (13); acute leukemia (14); carcinoma (with or without metastases) of breast, lung, kidney, ovary, prostate, and bladder (3, 15-16); milk-alkali syndrome (17-19); vitamin D intoxication (20-22); acute osteoporosis of immobilization associated with poliomyelitis, fractures, or Paget's disease (23-25); idiopathic hypercalcemia of infancy (26-28); adrenal insufficiency (29-31); and sarcoidosis (2, 32).

Hypercalcemia in sarcoidosis was first reported by Harrell and Fisher (1939) to occur in six of eleven biopsy proved cases (32). The etiology of this hypercalcemia has been the subject of much controversy. Localized bone destruction secondary to sarcoid involvement, parathyroid overactivity, and hyperproteinemia have been postulated. However, bone involvement demonstrable by x-ray is uncommon (33) and rarely seen in association with hypercalcemia and nephrocalcinosis (1, 34, 35). Parathyroid enlargement has rarely been found when looked for at operation (36) although there are case reports of this in the literature (37, 38). The diagnosis of hyperparathyroidism occurring simultaneously with sarcoidosis was made in the interesting case of Burr *et al.*, when cortisone failed to influence urinary and serum calcium (38). The response to cortisone has been stressed as a diagnostic aid in differentiating sarcoidosis and hyperparathyroidism, there being no change in calcium excretion in hyperparathy-

roidism (39). It might be mentioned here that the finding of a low phosphorus, which points strongly to hyperparathyroidism, is very rarely seen in sarcoidosis. Although serum protein alterations occur frequently in sarcoidosis they cannot be correlated with hypercalcemia (32) and the work of the Gutmans has shown that the protein bound fraction of the serum calcium is largely attached to albumin, whereas in sarcoid (40) the globulins are elevated.

In 1954, two separate groups of investigators demonstrated decreased fecal excretion of calcium in sarcoid patients by means of careful metabolic studies (33, 41). Anderson *et al.* felt that a decreased endogenous excretion of calcium into the feces could not quantitatively account for their results and there was, therefore, excessive absorption of calcium. This bore a close resemblance to the action of vitamin D, especially since the accompanying hypercalcemia suggested decreased renal tubular reabsorption. It had been shown also that whereas 160,000 units of vitamin D daily did not adversely affect normals (42), in some sarcoid patients even smaller doses caused rapid development of hypercalcemia (43, 44). In Case #1 of Anderson *et al.* serum calcium rose from 12.6 mg per cent to 16.3 mg per cent after twelve days of 9,000 units of vitamin D daily. These authors postulated an abnormal sensitivity to vitamin D in some patients with sarcoidosis (41). Henneman and associates showed increased calcium absorption by similar techniques but they postulated production of a vitamin D like substance (33). In a later paper they suggested possible mechanisms; photosensitivity in such manner as to produce excessive vitamin D on normal actinic exposure; inability to inactivate vitamin D; formation of vitamin D like substances by intestinal flora (45).

In the severe form of idiopathic hypercalcemia of infancy an unusual sensitivity to vitamin D has also been postulated. Fellers and Schwartz (by means of the rachitic rat biopsy technique) found three infants with this disease to have serum vitamin D levels twenty to thirty times that of normal infants (28). Forfar and associates collected 51 pairs of simultaneous cholesterol and calcium determinations in fourteen infants with this malady and found that both increased. From this they postulated an abnormality in cholesterol metabolism with production of a substance with vitamin D activity (46). At least eight compounds other than vitamins D<sub>2</sub> and D<sub>3</sub> have antirachitic properties, among them a cholesterol derivative, an estrogen-related substance, and an abnormal adrenal hormone (47). Any one of these, or a yet unrecognized compound, may be the cause of idiopathic hypercalcemia in infancy or of the hypercalcemia in sarcoidosis.

Of great interest is the study reported by MacIntyre and Davidson whereby magnesium deficiency produced a secondary potassium depletion, sodium retention, nephrocalcinosis, and hypercalcemia in rats (48). I am not aware of any studies on magnesium metabolism in sarcoid patients. All of these studies suggest new avenues of approach to the problem of hypercalcemia in sarcoidosis.

It is of interest that the patient reported drank two or more quarts of milk daily and that this may have been a precipitating cause of hypercalcemia. A high calcium intake and 800 to 1,200 units of vitamin D daily would be thus

provided. Case #3 of Anderson *et al.* (41), and Case #5 of Scholz (49) both drank large quantities of milk in association with vitamin D capsules and sodium bicarbonate respectively. The dietary histories of previously reported patients with respect to calcium and vitamin D have been scanty, although it is known that most patients with normocalcemic sarcoidosis do not seem abnormally sensitive to vitamin D (43, 50). Why some patients with sarcoidosis should develop this hypersensitivity and hypercalcemia is not known. There are no clinically recognizable differences in these patients in the cases reported thus far.

Renal failure occurring in the course of sarcoidosis was originally attributed to granulomatous involvement of the kidneys and on one occasion such a lesion responding to cortisone both functionally and histologically was described (51). However, massive granulomatous change sufficient to cause renal failure is rare; the autopsy lesions generally are of a focal nature and not extensive (36, 52). While such lesions may occasionally be present in the kidney with nephrocalcinosis, it is doubtful that they are the cause of renal failure although they may be contributory. It is currently believed that hypercalcemia and nephrocalcinosis are more important determinants of renal function in sarcoidosis.

In man and the experimental animal, it is known that hypercalcemia may produce impaired renal function with loss of concentrating ability (53-56). In animals this has been shown to occur both with and without demonstrable calcifications in the kidney (57, 58). The site of water reabsorption and urine concentration is in the collecting tubule and occurs secondary to medullary hypertonicity induced by sodium absorption in the loop of Henle (59). As the urine in the collecting ducts passes through the increasingly hypertonic medulla, water moves from the tubules into this hypertonic area. Concentration of the urine is thus achieved. Manitius *et al.*, produced hypercalcemia in rats and found a diminished concentration of sodium in the renal medulla. They also found histologic lesions in the collecting ducts, distal convoluted tubules, and loops of Henle. They felt that these lesions impaired concentrating ability by interfering with the absorption and concentration of sodium (60). Hypercalcemia may therefore impair the efficiency of the mechanism by which sodium is pumped out of the loops of Henle and concentrated in the medulla. The sodium diuresis induced by intravenous calcium infusion supports this theory (56). An alternative mechanism is that back diffusion of water from the collecting duct lumen into a hypertonic interstitium is impaired by the hypercalcemia-induced lesions in these ducts.

Löfgren and associates described sixteen cases of sarcoidosis studied with renal biopsies, six of whom had hypercalcemia (61). Of these six, five had impairment of concentrating ability and nephrocalcinosis. The sixth had normal renal function and no calcium deposits in the kidney. A recent case report suggests that the loss of concentrating ability may be more closely related to mineral salt deposits in the kidney than to hypercalcemia, but the available experimental evidence shows this may occasionally occur without nephrocalcinosis (62).



The relationship between hypercalcemia and nephrocalcinosis was firmly established by Klatskin and Gordon in their analysis of two cases of nephrocalcinosis and renal failure simulating hyperparathyroidism (36). The sequence of events consisting of hypercalcemia leading to nephrocalcinosis and then renal insufficiency with azotemia has been repeatedly stressed. Why some patients with hypercalcemia develop this complication and others do not is unknown. Vitamin D has long been known to produce structural damage in kidneys with severe impairment of function. Randall has suggested that calcium is desposited as a consequence of some form of renal tubular damage (64). Epstein *et al.*, showed that calciferol produces lesions predominantly in the collecting tubules associated with calcifications (57). W. A. D. Anderson has described tubular destruction, interstitial fibrosis, and glomerular atrophy occurring secondary to calcium deposition in and around renal tubules in hyperparathyroidism (65). The most likely mechanism is that hypercalcemia leads to tubular damage and that this damage causes alterations locally, allowing calcium to be precipitated. Barr, in an extensive review, stated that calcium concentration, phosphate concentration, degree of alkalinity in serum and tissue fluids, and local tissue factors were of importance in the precipitation of calcium salts (66).

Nephrocalcinosis, which has been reported as occurring in most of the disease states causing hypercalcemia, is in all probability secondary to prolonged elevations in serum calcium levels. However, on rare occasions calcium levels in nephrocalcinosis may be normal either as a transitory phenomenon or secondary to renal retention of phosphorus. Davidson, in his partial review of the subject, collected ten cases of nephrocalcinosis in sarcoidosis from the literature and added seven of his own collected from three large hospitals (67). Since then many more cases have been reported (34, 41, 61, 68-73), most notably Scholz's series from the Mayo Clinic (49, 69, 71). Males have predominated in these cases in contrast to the approximately equal proportion of males and females with sarcoidosis (49). The absence of concomitant pulmonary involvement, as in the case reported here, has been decidedly unusual. The incidence of clinically demonstrable chest lesions in sarcoidosis is 60 to 80 per cent and in the reported cases of nephrocalcinosis approximately 95 per cent.

The effect of cortisone on the manifestations of sarcoidosis has been amply demonstrated. Its effect on the correction of hypercalcemia was first described by Shulman *et al.* in 1952 (72) and since that time numerous reports on the salutary effect on hypercalcemia and renal function in sarcoidosis have appeared (41, 69, 71, 73). Serum calcium levels quickly revert towards normal in most cases, with restoration of concentrating ability and decreases in blood urea nitrogen and creatinine levels. This change may occur in a week or two, however, often without change in x-ray or biopsy appearance of the kidneys. It is generally necessary to keep patients on maintenance dosage of steroids in order to prevent recurrence, although in the two cases reported by Phillips and Fitzpatrick the serum calcium levels were normal 2½ years and 72 days respectively after cessation of steroid treatment (73). Bjorneboe *et al.* have shown

that the anatomic lesions of nephrocalcinosis are reversible, with dissolution of tubular calcifications within three weeks in a case of vitamin D intoxication (74). Danowski and his associates have shown the same to be true of subcutaneous calcifications (22). It therefore seems reasonable to assume that continued steroid therapy may result in the disappearance of microscopic calcifications if continued over long periods of time.

The mechanism of the steroid effect on hypercalcemia has been suggested by numerous workers. It has been shown that cortisone increases fecal excretion of calcium and as the plasma calcium decreases, urinary calcium excretion also falls (41, 45, 49). Soffer has suggested that cortisone markedly increases fecal excretion of calcium and he felt this was due to increased excretion and not just decreased absorption (75). Other workers have also shown an increased calcium excretion following cortisone therapy, although whether this is due to decreased absorption or increased endogenous excretion is not certain (41, 45, 49, 76). Fischer and Hastrup have shown that cortisone may induce a negative calcium balance which can be reversed to near normal by calcium and vitamin D (77). Some patients with Cushing's disease appear to have a decreased intestinal absorption of calcium which is not overcome by a high calcium diet and vitamin D (78). Cortisone has precipitated tetany in three cases of sprue (79) and has been shown to increase the vitamin D requirements of hypoparathyroid patients controlled on tachysterol (80). Connor *et al.* have shown that in one patient with vitamin D intoxication the hypercalcemia could be corrected, even though the intoxicating dose of vitamin D was continued concomitantly with the cortisone (81). Sprague has demonstrated that the increased serum calcium sometimes seen after adrenalectomy for Cushing's disease is reversed by cortisone (31). Selye has shown that cortisol prevents nephrocalcinosis in adrenalectomized rats (82).

From studies such as these it has been suggested that cortisone may competitively inhibit the effect of the hypercalcemia-inducing substance at the site of intestinal absorption. Certainly the structures of vitamin D and cortisone are sufficiently similar to make this possibility feasible. An indirect result on calcium metabolism secondary to the action on sarcoid granulomas has also been postulated but definite proof is lacking (68).

Glycosuria and a typical diabetic glucose tolerance curve were present in the case herein reported. The completely negative familial history of diabetes mellitus raises the possibility of sarcoid involvement of the pancreas sufficient to cause diabetes. The association of diabetes mellitus and sarcoidosis has been reported by Eckelund (83) and was present in Case #2 of Henneman *et al.* (45) and in the case reported by Scholz (71). No etiologic relationship was suggested. Only two cases of pancreatic involvement were found in Longcope and Freiman's series and these were asymptomatic (34). In autopsy cases pancreatic lesions have generally been few in number and almost always insignificant (34, 52, 84). As glucose tolerance tests in patients with sarcoidosis with or without nephrocalcinosis are infrequently reported in the literature, one can only specu-

late on the etiology and frequency of this relationship. There appears to be no increased incidence of diabetes mellitus in other hypercalcemic states, making it unlikely that elevated blood calcium levels have any etiologic role.

#### SUMMARY

A patient with hypercalcemia, nephrocalcinosis, and renal failure occurring in association with sarcoidosis is described.

The mechanism of hypercalcemia in sarcoidosis as well as its effect on renal function is reviewed.

Prednisone corrected the hypercalcemia and improved kidney function, as has been previously reported. The theories as to the mechanism of this action are mentioned.

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## GAUCHER'S DISEASE AND ACUTE LEUKEMIA

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The association of Gaucher's disease and acute leukemia in the same individual has not been recorded in the literature. We are reporting two adult patients with this combination:

### CASE 1

H.B., a 60 year old white Jewish male salesman, was admitted to The Mount Sinai Hospital in September, 1953 for repair of a recurrent right inguinal hernia. The physical examination was unremarkable, except for a palpable liver edge 2 fingerbreadths below the right costal margin, and the right inguinal hernia. A urinalysis was normal. The hemoglobin was 12.5 Gm per cent. A right inguinal herniorrhaphy was performed without incident, and the patient was discharged on the eighth hospital day.

He was readmitted to the hospital in July, 1956 because of weakness, angina pectoris and dizzy spells of one week's duration. He stated that he had been in good health until the present illness. Family history was negative for hereditary diseases. Physical examination revealed marked pallor. The blood pressure was 140/80 and pulse 96, regular. The liver and spleen were palpable 2 fingerbreadths below the right and left costal margin respectively. The prostate was 2+ enlarged, smooth and without nodules.

The admission hemoglobin was 6.4 Gm per cent. The white cell count was 10,400 with the differential smear revealing mature granulocytes 15%, band forms 25%, lymphocytes 18%, monocytes 4%, promyelocytes 9%, myelocytes 7%, blast forms 8%, atypical lymphocytes 13% and normoblasts 1%. Bone marrow aspiration showed Gaucher's disease and myelocytic leukemia. The marrow revealed large cells with pale staining cytoplasm and eccentrically placed nuclei, typical of Gaucher cells. In addition, there was a diffuse infiltration of primitive cells of the granulocytic series. The hematology diagnosis was Gaucher's disease with myelocytic leukemia. Serum acid phosphatase values ranged from 7.7 to 10.1 Gutman units.\* The serum alkaline phosphatase was 5.9 King-Armstrong units, Coombs test was negative and the total bilirubin was 1.1 mg%.

X-rays of the skull, pelvis, and long bones revealed lacunae of the inner aspect of the cortex in most bones surveyed, not having the appearance of metastatic or myeloma deposits. An upper gastrointestinal series, barium enema and chest x-ray were normal.

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\* Tuchman *et al.* have demonstrated that serum acid phosphatase is increased in Gaucher's disease (1).

The patient was transfused with whole blood and discharged taking prednisone 30 mg daily. He continued to work and in September 1956 6-mercaptopurine was added in doses of 150 mg daily for one week. The white cell count fell from 30,000 to 12,000 but progressive anemia was noted, for which he received whole blood transfusions.

The last hospital admission occurred in November 1956, because of chills, fever and cough of four day's duration. Physical examination revealed temperature of 103° F., blood pressure of 100/55, regular pulse of 112 per minute, and labored respirations of 40 per minute. The skin was pale and covered with numerous petechiae. Pungueculae of the right eye were noted. The liver was 6 fingerbreadths below the right costal margin. The spleen was 2 fingerbreadths below the left costal margin. There was a firm 2 × 2 cm right inguinal node, but no other lymphadenopathy was present. Auscultation of the lungs showed diminished breath sounds at the left base and scattered rhonchi. The chest x-ray demonstrated a pneumonic infiltration of the left lower lobe.

The hemoglobin was 7.5 Gm per cent. The white cell count was 150,000 with the differential smear revealing mature granulocytes 6%, band forms 4%, metamyelocytes 10%, myelocytes 56%, blast forms 10%, lymphocytes 4%, monocytes 8%, and normoblasts 2%. The platelet count was 48,000. Bone marrow aspiration revealed the picture of acute granulocytic leukemia and Gaucher's disease (80% blast forms and scattered Gaucher cells). Other laboratory data were: Sedimentation rate 86 mm in one hour, blood urea nitrogen 51 mg%, creatinine 1.5 mg%, fasting blood sugar 123 mg%, calcium 9.0 mg%, phosphorus 4.2 mg%, serum acid phosphatase 14.8 Gutman units, total bilirubin 4.2 mg%, serum alkaline phosphatase 28 King-Armstrong units, prothrombin time 18 seconds (control 12 seconds), and cephalin flocculation 4+. Urinalysis showed a 1+ albumin with 3 to 4 red blood cells, and 5 to 6 white blood cells per high power field. The pneumonia responded to penicillin therapy, prednisone was continued and treatment with 6-mercaptopurine, 400 mg daily, was instituted with gradual reduction in dosage to 50 mg daily by the second week. The white cell count fell to between 10,000 and 15,000. The patient developed a salmonella septicemia which responded to intravenous chloromycetin. He also developed a staphylococcus aureus parotid gland abscess which was resistant to antibiotics, surgical drainage and radiotherapy. Anemia progressed despite numerous blood transfusions and generalized purpura occurred with a platelet count of 7,000. He lapsed into coma and expired on the 40th hospital day. Permission for autopsy was not granted.

## CASE 2

I. W., a 55 year old white Jewish male advertising executive, was examined in December 1957, before undergoing suprapubic prostatectomy. He had been under treatment by a urologist for 2½ years because of severe symptoms of prostatism and a markedly enlarged prostate. Hematuria had been present intermittently during this period, but no other spontaneous bleeding was present. The intravenous pyelogram was normal except for the prostate enlargement. The patient had known of an enlarged spleen for at least seven years. Family



history was negative. The pertinent physical findings were pingueculae bilaterally, a diffuse tannish pigmentation of the exposed areas of skin, a liver edge palpable 2 fingerbreadths below the right costal margin, a spleen palpable 3 fingerbreadths below the left costal margin, and a 4+ enlarged prostate. The blood pressure was 140/80, pulse 80 and regular. Hematological evaluation demonstrated a hemoglobin of 13.7 Gm %, red cell count 5.4 million, hematocrit 46%, white cell count 9,300 with a differential smear of mature granulocytes 54%, lymphocytes 38%, monocytes 4%, eosinophils 2% and basophils 2%. The platelet count was 30,000, no clot retraction, coagulation time 17½ minutes, prothrombin time 13 seconds, and serum prothrombin time 14 seconds. The bone marrow was hypercellular, with a diffuse infiltration by the typical Gaucher cells as described in the previous case. Megakaryocytes were present in adequate numbers and except for 19% lymphocytes, there was no other abnormality of the marrow elements. The thymol turbidity was 7.2 units, cephalin flocculation 2+ and gamma globulin 1.88 Gm %. X-rays of the long bones did not show abnormalities. Because of the bleeding tendency, operation was withheld, but the symptoms of prostatism progressed to episodes of acute urinary retention. In June 1958, he was admitted to The Mount Sinai Hospital for a suprapubic prostatectomy. The liver enlargement was now 3 fingerbreadths and the spleen was palpable 4 fingerbreadths below the costal margins. The remainder of the physical examination was unchanged. In particular, there was no significant lymphadenopathy.

The hemoglobin was 12.8 Gm %, red cell count 5.1 million, hematocrit 43%, white cell count 61,000 with mature granulocytes 14%, and lymphocytes 86% (consisting of many atypical forms and occasional blasts). The platelet count was 20,000. Bone marrow aspiration now revealed clusters of typical Gaucher cells and an infiltration with lymphoid cells (lymphocytes 33%, "hematogones" 6.5%, lymphoblasts 1.5%) resembling chronic lymphocytic leukemia. The patient received a platelet transfusion pre- and postoperatively. The suprapubic prostatectomy was performed by Dr. H. Evans Leiter and with careful hemostasis there was a minimum of additional bleeding. The pathologic diagnosis was fibroadenoma of the prostate.

He felt well enough to return to work in July, but in August 1958, was admitted to The Long Beach Memorial Hospital with a low grade fever, anorexia and lethargy. There had been a 15 pound weight loss in four weeks. The temperature was 101°F, pulse 100 regular, blood pressure 130/80. Small firm nodes were palpable in the anterior and posterior cervical chains. The spleen was now enlarged to the pelvic brim and the liver was 4 fingerbreadths below the right costal margin. Numerous petechial showers were found on the lower extremities. The hemoglobin was 8.6 Gm %, platelet count 50,000, white cell count 11,500 with mature granulocytes 20% and lymphocytes 80% (consisting of many primitive and blast forms). Bone marrow aspiration revealed lymphoblasts 25%, lymphocytes 24% and "hematogones" 7%. The reticulocyte count was 1.2% and the serum bilirubin was normal. Urine, blood and bone marrow cultures were nega-

tive, as were serologic tests for febrile agglutinins, influenza, atypical pneumonia, heterophile antibodies and the Coombs test. An upper gastrointestinal series was normal.

The low grade fever was believed to be due to acute lymphoblastic leukemia. The patient received blood transfusions and was started on prednisone 100 mg daily. Fever subsided within three days and the spleen decreased to 4 finger-breadths below the left costal margin at discharge on the 13th hospital day. However, he developed diabetes mellitus and oral moniliasis, necessitating gradual reduction of prednisone. He was fairly well and able to work for two months while maintained on prednisone 25 mg daily and tolbutamide 2 Gm daily. In October 1958, the hemoglobin was 13.1 Gm %, red cell count 5.5 million, platelet count 50,000, and white cell count 16,700 with 35% mature granulocytes and 65% lymphoblasts and lymphocytes. However, the spleen increased in size to the pelvic brim and did not respond to 1,200 roentgens delivered in a period of two weeks in November, 1958. In addition, the patient developed bilateral thrombophlebitis of the thighs and a 4+ pitting edema of the lower extremities. Chlorothiazide 1 Gm daily and a low salt diet partially controlled the edema. Fever recurred, generalized lymphadenopathy and enlargement of the hilar lymph nodes on chest x-ray was noted in December 1958, and the prednisone was rapidly increased to 200 mg daily and then to 300 mg daily, with no response of the clinical or hematological status. The patient was readmitted to The Long Beach Memorial Hospital in January 1959, with temperature of 101°F, marked pallor with multiple petechiae and ecchymoses of the skin, oral moniliasis, diffuse lymphadenopathy and liver enlargement to the right iliac crest. The spleen occupied the entire left side of the abdomen. There was a 4+ pitting edema of the lower extremities. The blood pressure was 100/70, pulse was 120 and regular; auscultation of the heart and lungs was negative. The hemoglobin was 9.0 Gm %, white cell count 3,000 with 90% lymphocyte and blast forms, and platelet count 10,000. The Coombs test was negative. He required 60 units of xpi insulin daily to prevent acidosis. Whole blood transfusions, antibiotics, and chlorambucil 12 mg daily were administered. There was no improvement and on the fifth hospital day he developed massive hemoptyses and expired.

Autopsy performed by Dr. Leo Meyer revealed:

- A. Lymphatic leukemia (spleen, liver, lymph nodes and bone marrow)
- B. Gaucher's disease (spleen, liver, lymph nodes and bone marrow)
- C. Hemorrhagic infarction, right lower lobe of the lung with a hemorrhagic pleural effusion
- D. Left pleural effusion
- E. Pulmonary congestion and edema, early bronchopneumonia
- F. Active peptic ulcer, pylorus, with surface *Monilia albicans* infection
- G. Peptic esophagitis with surface *Monilia albicans* infection
- H. Multiple renal and splenic infarcts
- I. Suprapubic prostatectomy, status postoperative, remote
- J. Multiple petechiae and purpuric spots of the skin and mucous membranes

The spleen weighed 2000 Gm and the liver 1650 Gm. Early atheromatous plaques were present in the ascending and descending portions of the aorta. The coronary vessels were patent throughout.

#### DISCUSSION

Rare combinations of multiple diseases in the same individual should be recorded since these reports may provide information as to the potential effect of the diseases upon each other. Furthermore, clarification of a possible genetic disturbance may be forthcoming in the simultaneous occurrence of two congenital diseases, as suggested for mongolism and congenital leukemia (2-4).

The first two patients in the literature of Gaucher's disease associated with acute leukemia are reported in this paper. Patient H.B. suffered from an acute granulocytic leukemia. Patient I.W. was originally considered to be a case of chronic lymphatic leukemia but a rapid transition to a downhill course occurred, more in the nature of an acute lymphocytic leukemia or fulminant lymphosarcomatosis. Large doses of prednisone, as has been suggested by Granville, *et al.*, (5) produced a transient partial remission but side effects of diabetes mellitus, moniliasis, gastrointestinal ulceration, thrombophlebitis and edema were troublesome. Reinstitution of higher doses, once the acute leukemia became progressive again, did not affect the course of the disease.

#### SUMMARY

Two cases of Gaucher's disease associated with acute leukemia are reported. This is the first time that this combination has been recorded in the literature.

#### ACKNOWLEDGMENTS

We are grateful for the hematologic consultations in Case 2 of Dr. Stanley L. Lee, then of The Mount Sinai Hospital, New York, N. Y., and Dr. William Damashek, of The New England Center Hospital, Boston, Mass.

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# PERCUTANEOUS CATHETERIZATION OF THE AORTA\* †

## IN THE DIFFERENTIAL DIAGNOSIS OF LEFT-TO-RIGHT SHUNTS AT THE BASE OF THE HEART

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Although individual diagnostic procedures utilizing the passage of a catheter into the aorta are often performed, the full potential of aortic catheterization is not often realized. It is the purpose of this communication to emphasize that the uses of the catheter as a probe, for recording of pressures, for the purpose of injecting dye during indicator dilution studies, and for sampling of blood for oxygen analysis, all modalities in common use in right heart catheterization, are equally applicable to aortic catheterization. Furthermore, many of these studies may be performed percutaneously, with avoidance of the technical difficulties and possible complications of arterial exposure and incision. Technical details of percutaneous catheterization of the aorta will be described together with three illustrative cases.

### METHODS

A VXO20 (Becton, Dickinson) plastic catheter was the first type we utilized for aortic catheterization. It was passed through a #18TW needle. The tubing was filled with 70% Urokon to make it radiopaque. Spot x-ray films were taken for positioning of the tip of the catheter in the aorta, because the catheter could not be seen well fluoroscopically. The disadvantages of this catheter were that blood samples could not be drawn; the tip of the catheter frequently moved after initially being positioned; and the lumen was so small that any breach of technique resulted in damped tracings.

Next, a larger size catheter of the same material as above (VXO28) was employed which could be passed through a #16TW needle. This catheter was also filled with radiopaque solution, but was likewise poorly visible fluoroscopically, and would not maintain its position. Blood specimens could be obtained and pressure recording was more reliable than with the smaller catheter. However, in recording pressures the radiopaque solution was lost, and had to be reinjected for later fluoroscopy.

An Afford\*\* radiopaque vinyl plastic catheter was then used which could be

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† This investigation was supported in part by research grant #H-2168 and fellowship #HF-8241 (Dr. Henry) from the National Heart Institute, United States Public Health Service.

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seen fluoroscopically, but with some difficulty. As with the B-D catheters, the Afford catheter was filled with heparin (50 mg/cc) and the end plugged with a sawed-off pin. Depending on its size, the catheter was passed through a #16 or #18TW needle via the right brachial artery or right femoral artery. When the tip of the catheter was in the desired location, the needle was removed over the catheter and the pin withdrawn. The end of the catheter was attached by a Tuohy-Borst adapter to a three-way stopcock, which was in turn connected to the transducer and heparinized infusion.

There were several difficulties with the Afford technique. When passed through the right brachial artery, the catheter frequently met an obstruction in the region of the origin of the innominate artery. Because of the rigidity of the catheter, it often could not be passed beyond this point. By contrast, the passage of the more pliable B-D catheters was seldom obstructed in that location. Furthermore, because the catheter would not hold a curve at the tip, it was often impossible, when coming from the femoral artery, to pass the catheter into the ascending aorta. Only cold sterilization of these catheters was possible and it was found that after they were sterilized several times the catheters became brittle.

We now often use an Ödman-Ledin radiopaque polyethylene tubing (1) in a modification of the Seldinger technique (2). The heparin-filled catheter is passed over a metal leader with a flexible tip which has been introduced into the artery through a #16TW needle. The tip of the leader protrudes beyond the catheter, and both are passed to approximately the desired site when the leader is withdrawn and a heparinized infusion started. The catheter alone is then passed under fluoroscopic control the short remaining distance. The opacity of the metal leader aids in fluoroscopic visualization, and the flexible metal tip increases maneuverability. It is possible to mold the Ödman-Ledin catheter into a desired shape, which will subsequently be resumed after removal of the metal leader from the catheter in the aorta. In this way, the curved catheter tip may easily be guided into the ascending aorta when passed from below.

Percutaneous aortic catheterization as described above is not without risk. We have encountered temporary ischemia of an extremity, due, in most cases, to spasm. On one occasion following passage of an Ödman-Ledin catheter, thrombosis of the femoral artery occurred. Fortunately there were no permanent sequelae in any of these cases.

We employ an Electronics for Medicine oscilloscopic 8-channel recorder. Statham P23G transducers are routinely used. The infusion bottles are connected by rubber tubing to a pressure can reservoir. A special Abbott disposable infusion tubing is used. An adaptor screw top for the infusion bottle made by George R. Pilling and Son permits high pressure to be transmitted from the pressure reservoir without leakage from the bottle. Dye dilution studies are performed with the Colson densitometer employing a constant flow motor-driven syringe. Indigo carmine dye is routinely used.

## CASE REPORTS

*Case No. 1*

N.L., a 22 year old female, entered The Mount Sinai Hospital in January, 1959 for evaluation of a cardiac murmur known since birth. Her growth and development were normal. In Italy, at the age of twelve she was treated for "poor heart action" with digitalis. This was discontinued after a few years. Her primary complaints were palpitations with exercise, exertional dyspnea, and easy fatigability.

On physical examination there was no cyanosis or clubbing of the upper or lower extremities, and the positive features were limited to the cardiovascular system. The blood pressure was 100/65. The ventricular rate was 65 per minute and the rhythm regular. The apical impulse was palpable in the 5th intercostal space inside the midclavicular line. There was an obvious left precordial bulge. A high-pitched midsystolic murmur was heard at the 2nd intercostal space to the left of the sternum followed by a loud, snapping, prolonged pulmonic second sound. A long, high-pitched, decrescendo diastolic murmur followed the second sound and was also heard best in the 2nd intercostal space to the left of the sternum (Fig. 1). It was apparent that the murmur was not a continuous one characteristic of uncomplicated patent ductus arteriosus. Rather, the diastolic component was considered to be due to pulmonic insufficiency.

Fluoroscopy demonstrated increased hilar pulsations and marked prominence of the main pulmonary artery and secondary branches. The x-ray film of the chest (Fig. 2) likewise showed the prominence of the pulmonary artery and its branches. The standard twelve lead electrocardiogram demonstrated a right ventricular hypertrophy pattern with right axis deviation in the limb leads, RS in lead V1 and RS in lead V6. The vectorcardiogram demonstrated the QRS loop entirely displaced anteriorly but with counter-clockwise rotation in the horizontal plane, a pattern seen in biventricular hypertrophy.

The results of cardiac catheterization are seen in Table 1. Pulmonary hypertension was found with a left-to-right shunt into the pulmonary artery. Femoral arterial blood was slightly unsaturated (90%).

To establish the anatomical location of the shunt, the aorta was catheterized from the right femoral artery using an Afford radiopaque catheter passed through a #16TW needle after percutaneous puncture of the vessel. The catheter was advanced to the arch of the aorta where 4 cc of indigo carmine dye was injected. The dye-containing blood was sampled from the left femoral artery through a Courmand needle which was attached by means of polyethylene tubing to the Colson densitometer. A similar injection was made at a site 3 to 4 inches downstream. In addition, blood samples for oxygen analysis were withdrawn at several levels in the aorta in rapid succession (Table 1).

The dye-dilution curve recorded after injection of dye at the level of the aortic arch indicated an abnormal initial curve of low amplitude followed by an early recirculation curve. A normal curve was recorded when the dye was injected below this level (Fig. 3). The oxygen values indicated a modest degree of right-to-left shunt through the aorticopulmonary communication as shown by the mild unsaturation of the samples drawn from below the level of the aortic arch. The sample of blood drawn from the aorta proximal to the level of the aortic arch was fully saturated indicating that the right-to-left shunt was distal to that point.

The initial catheterization established the presence of an aorticopulmonary communication with predominant left-to-right shunting of blood. By means of more refined techniques including the use of indicator dye studies from the aorta and blood sampling at selected sites in the aorta, the left-to-right shunt was localized to a patent ductus arteriosus since it occurred through an anatomical communication distal to the arch of the aorta. In the presence of pulmonary hypertension with only minimal right-to-left shunting through the patent ductus arteriosus, the patient was operated upon at the Columbus Hospital, New York on April 1, 1959 and a large communication, the same diameter as the descending aorta, was ligated

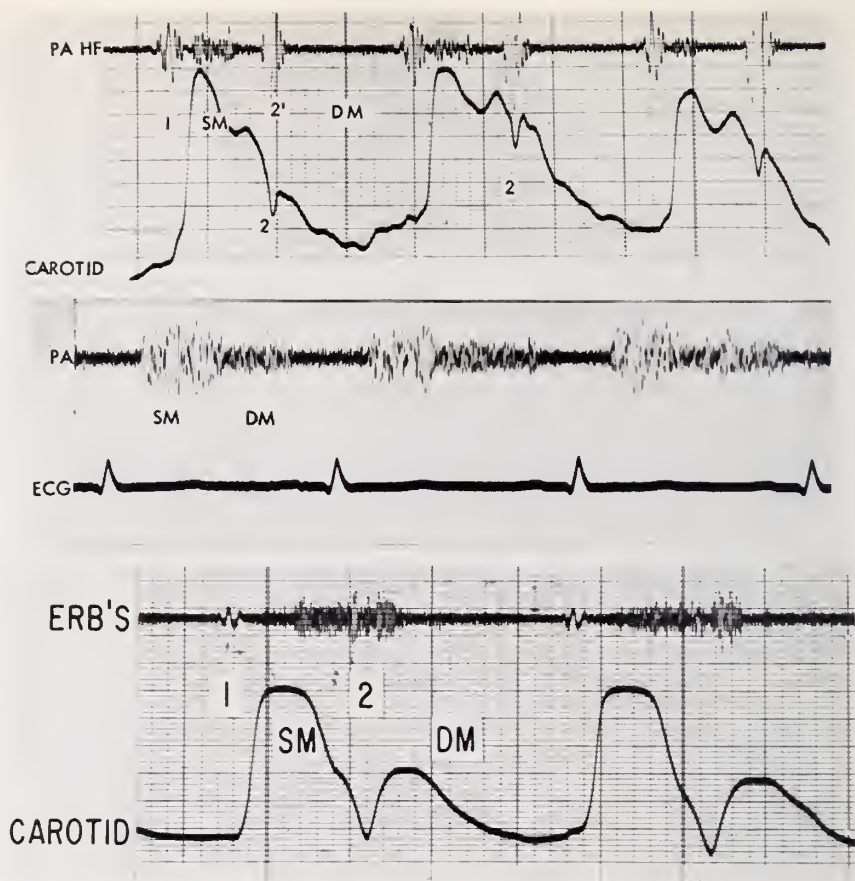


FIG. 1. Phonocardiograms.

Top—Case 1 (N.L.). Midsystolic high frequency murmur, loud pulmonic component of 2nd sound, low frequency holodiastolic murmur.

Middle—Case 2 (A.P.). Machinery murmur.

Bottom—Case 3 (E.K.). Machinery murmur, crescendo systolic, decrescendo diastolic. (Pa—Pulmonary Artery area; SM—systolic murmur; DM—diastolic murmur; 2—dirotic notch of carotid pulse and aortic component of 2nd sound; 2'—pulmonic component of 2nd sound).

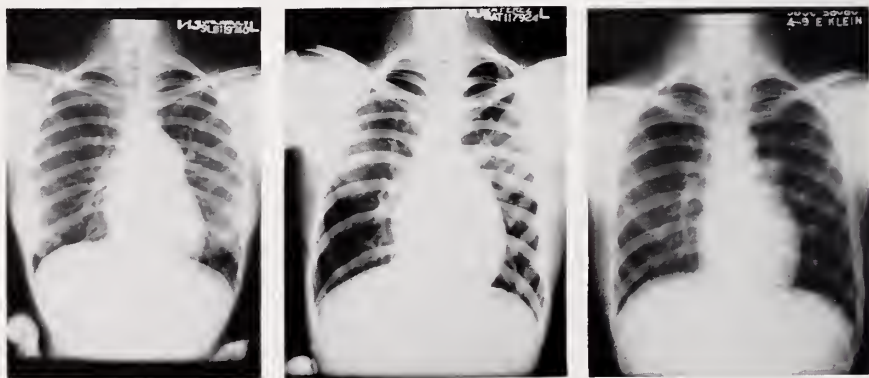


FIG. 2. P.A. Films of the chest.

Left—Case 1 (N.L.). Markedly enlarged main pulmonary artery with prominence of central and peripheral pulmonary blood vessels.

Middle—Case 2 (A.P.). Increased transverse diameter of heart with prominence of left cardiac contour, enlarged main pulmonary artery with prominent hilar vessels.

Right—Case 3 (E.K.). Fullness of the cardiac silhouette with slight increase in central pulmonary vascular markings.

TABLE 1  
Summary of Cardiac Catheterization Findings (N.L.)

	Site	O <sub>2</sub> Content (Volumes %)	O <sub>2</sub> % Saturation	Pressure (mm/Hg)
1/14	Superior Vena Cava	11.5	63	
	Inferior Vena Cava	12.7	70	
	Right Atrium			
	high	12.1	66	3 mean
	mid	12.0	66	
	low	12.6	69	
	Right Ventricle			
	tricuspid valve	12.5	68	98/5
	mid	12.7	70	
	outflow	13.1	72	
	Main Pulmonary Artery	14.1	77	98/52 (75)
	Right Pulmonary Artery	14.3	78	
	Left Pulmonary Artery	14.7	81	11 mean
	Pulmonary Capillary Venous "Wedge"			
	Right Femoral Artery	16.5	90	
	Capacity	18.7		
1/16	Aortic Arch	16.9	98	
	Descending Aorta—3 inches below	15.9	92	
	Left Femoral Artery	15.8	92	
	Capacity	17.5		

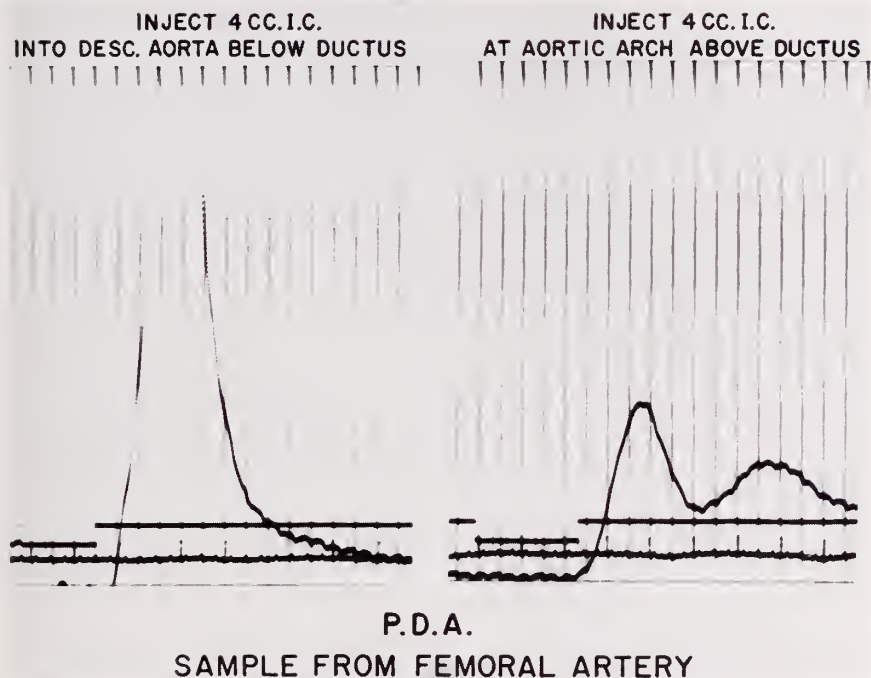


FIG. 3.

(Case 1) Dye curves sampled from femoral artery after injection proximal and distal to site of ductus arteriosus. The first curve after injection of dye into descending aorta, is normal. The low initial curve after injection from the level of the aortic arch represents shunting of dye-containing blood through the patent ductus arteriosus. Some dye also entered the left subclavian artery as indicated by a change in color of the left hand. An early recirculation curve represents return of shunted dye-containing blood to the sampling site. (Time lines = 1 sec.)



by Dr. Santo Finocchiaro. At this time, two years after surgery, there has been no marked improvement of her previous symptoms, and the Graham-Steell murmur of pulmonic insufficiency is still evident.

*Case No. 2\**

A.P., an 11 year old male, was admitted to The Mount Sinai Hospital for the first time in 1950 for evaluation of a cardiac murmur known from infancy. He was a "blue baby" at birth, and during the first few months of life had convulsive seizures and periods of cyanosis. His growth and development in early life were slow, but since then had been normal.

TABLE 2  
*Summary of Cardiac Catheterization Findings (A.P.)*

Site	O <sub>2</sub> Content (Volumes %)		Pressure (mm/Hg)	
	2/1/50	12/12/58	2/1/50	12/12/58
Superior Vena Cava	10.0	14.2		
Inferior Vena Cava		15.0		
Right Atrium				
high		14.0		
mid	11.6	13.3	1 mean	5 mean
low		15.0		
Right Ventricle				
tricuspid valve	12.0	13.8	35/0	
mid		15.3		44/5
outflow	12.0	15.0	35/0	
Main Pulmonary Artery	13.5	16.4	13/5	20/8 mean 12
Right Pulmonary Artery	13.7	15.6	10 mean	
Left Pulmonary Artery	13.3	15.7	18/9	23/12 mean 18
Arterial Catheter in mpa		16.4	simultaneously	17 mean
Venous Catheter in mpa		16.2		17 mean
Right Brachial Artery	16.5 (99% sat.)	18.3 (95% sat.)		
Capacity	16.9	19.6		

The original physical examination revealed a blood pressure of 96/50. The point of maximal impulse was in the 5th intercostal space outside the midclavicular line. There was a grade 4/4 harsh machinery murmur heard best in the 2nd and 3rd intercostal spaces to the left of the sternum. The murmur radiated to the left and into the neck. Systolic and diastolic thrills were palpable over the areas where the murmurs were heard best. The second pulmonic sound was slightly split and normal in intensity.

The electrocardiogram showed no axis deviation. An angiocardigram demonstrated a dilated main pulmonary artery. The structures distal to the bifurcation of the artery were poorly opacified, probably indicating a rapid dilution of the dye-containing blood in the main pulmonary artery by arterial blood entering from the aorta.

The results of cardiac catheterization can be seen in Table 2. There was a left-to-right shunt into the pulmonary artery which appeared to confirm the diagnosis of patent ductus arteriosus. Mild pulmonic stenosis was also noted.

At the time of surgery in February, 1950, no functioning patent ductus arteriosus was found. The ligamentum arteriosum was ligated and divided. A thrill was felt over the main pulmonary artery and conus portion of the right ventricle. The ascending aorta was enlarged

\* This case has been reported previously: *Am. J. Cardiol.* 5: 273, 1960.

one and one-half times its normal diameter. An aortic septal defect was suspected but not proved. (A report of this case was published at the time (3)).

The patient was readmitted to the hospital for further evaluation in December, 1958 at the age of 19, for it was felt that surgical correction of the defect was now feasible. Physical examination at this time revealed the blood pressure to be 140/58-40. The pulse was 80 per minute, regular, and collapsing in quality. Systolic and diastolic thrills were associated with a grade 4-4 machinery murmur heard loudest in the 3rd intercostal space to the left of the sternum (Fig. 1). A localized apical heave was palpated in the 6th intercostal space outside the midclavicular line.

The x-ray film of the chest showed enlargement of the left ventricular and left atrial chambers of the heart, and prominent main and secondary pulmonary artery branches (Fig. 2).

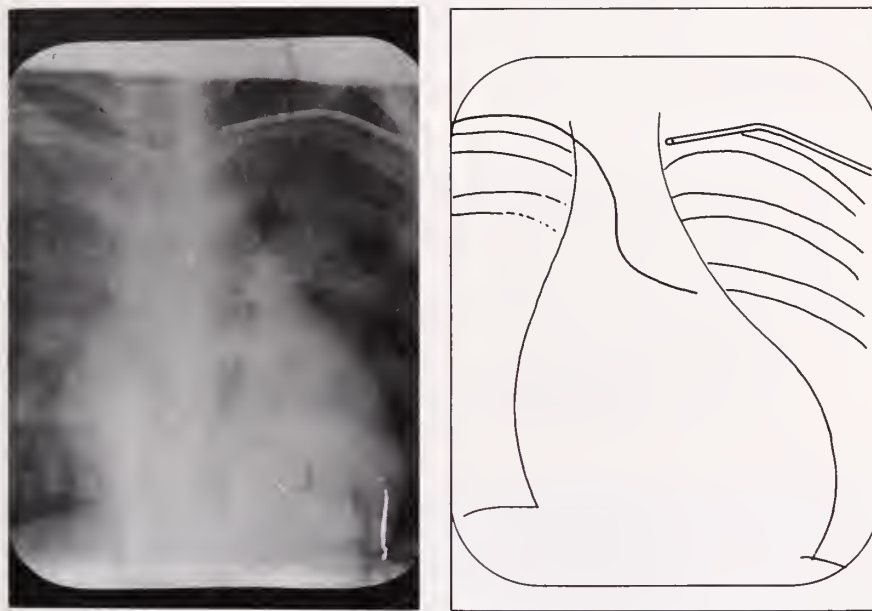


FIG. 4. (Case 2) Spot x-ray film to show catheter passing through aorticopulmonary defect into pulmonary artery. Because the original film was lacking in contrast, a drawing has been included.

The electrocardiogram revealed left ventricular hypertrophy. The vectorecardiogram showed a counter-clockwise inscribed qrs loop in the horizontal plane. The initial segment of the loop was anterior and to the right; the rest of the loop was posterior and to the left, a pattern seen in biventricular hypertrophy.

A second cardiac catheterization was performed. Initially, a Cournand catheter was introduced through a left antecubital vein and a standard right heart catheterization was performed. A radiopaque Afford catheter was then passed through a #16TW needle via percutaneous puncture of the right brachial artery and guided into the mediastinum. After entering the ascending aorta, the catheter curved sharply to the left and slightly downwards (Fig. 4). Simultaneous pressures were obtained through this catheter and that in the main pulmonary artery. The mean pressures were identical, although there was considerably more artefact in the pulses obtained through the right-sided catheter. Moreover, blood samples from both catheters revealed the same oxygen saturation (Table 2). A continuous pressure record was taken as the catheter was pulled back from the pulmonary artery to the aorta (Fig. 5).

It was evident that the Afford catheter had traversed an aorticopulmonary septal defect which appeared to have a take-off from the aorta at a rather high level. The catheterization results again demonstrated a left-to-right shunt into the pulmonary artery, and the mild pulmonic stenosis.

Surgery was performed by Dr. Ivan Baronofsky without the need for extracorporeal circulation although the pump oxygenator was available. Two separate adjacent aorticopulmonary communications were ligated and divided. It was not thought necessary to correct the mild pulmonic stenosis.

### Case No. 3

E.K., a 17 year old male, was first admitted to The Mount Sinai Hospital in 1955 for evaluation of a murmur known since birth. His growth and development had been normal.

Physical examination revealed a blood pressure of 120/80. A long, loud, systolic murmur was heard along the lower left sternal border accompanied by a systolic thrill. The murmur did not radiate into the neck. The second pulmonic sound was snapping and louder than the second aortic sound. No diastolic murmur was heard.

An x-ray film of the chest showed no evidence of chamber enlargement. There was slight

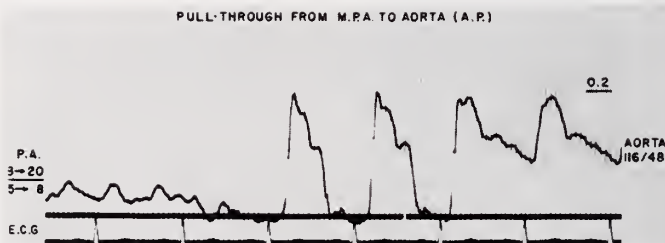


Fig. 5. (Case 2) Pressure recording as catheter tip was pulled back from pulmonary artery to aorta. The nature of the two transitional beats is not clear.

increase in prominence of the hilar vessels. The electrocardiogram and vectorcardiogram were normal.

The results of the cardiac catheterization can be seen in Table 3. They were interpreted as indicating the presence of an interventricular septal defect with normal pressures and a small left-to-right shunt.

In 1957, he was readmitted because of a marked change in the physical findings, although the patient had not developed any symptoms. A machinery murmur had now appeared where previously only a systolic murmur had been heard (Fig. 1). In addition, the x-ray film of the chest revealed a distinct increase in the prominence of the left ventricular contour (Fig. 2). A slight pulmonary artery convexity was seen. The electrocardiogram showed no change from the one recorded two years earlier.

Unfortunately, the oxygen studies obtained during cardiac catheterization were unsatisfactory because of technical difficulties. He was therefore readmitted for the third time in April, 1958. The blood pressure was 110/60. No change had occurred in physical findings, electrocardiogram, and x-ray film of the chest.

Cardiac catheterization was performed (Table 3) indicating an oxygen step-up first appreciated at the level of the right ventricle. Through a #16TW needle after percutaneous puncture of the right femoral artery, an Afford radiopaque catheter was passed into the aorta and 4 cc of indigo carmine dye was injected successively at sites just above the aortic valve, at the level of the transverse arch and in the descending aorta (Fig. 6). Dye-containing blood was sampled by the Colson densitometer through a Courmand arterial needle in the left femoral artery. The dye-dilution curve recorded after injection from the most proximal site was of lower amplitude and showed an earlier recirculation curve than the one recorded after

dye was injected from the level of the aortic arch. The slight abnormality of the dye-dilution curve after injection at the latter site can be explained by reflux of some dye towards the aortic valve. The curve written after the injection of dye into the descending aorta was normal (Fig. 7).

TABLE 3  
*Summary of Cardiac Catheterization Findings (E.K.)*

Site	O <sub>2</sub> Content (Volumes %)		Pressure (mm/Hg)	
	12/22/55	4/11/58	12/22/55	4/11/58
Superior Vena Cava	13.5	15.5		
Inferior Vena Cava	13.8			
Right Atrium				
high	13.6	15.4		
mid	11.7	16.0	6 (mean)	4 (mean)
low	13.9	16.6		
Right Ventricle				
tricuspid valve	14.7	18.1		
mid	15.0	18.2	22/6	30.0
outflow	15.5	17.7		
Main Pulmonary Artery	15.1	17.4	22/10	25/7
			(mean 17)	(mean 14)
Right Pulmonary Artery	15.0	17.6		
Pulmonary Capillary Venous "Wedge"			10 (mean)	10 (mean)
Peripheral Artery	18.3 (93% sat.)	19.1 (98% sat.)		
Capacity	20.1	19.8		

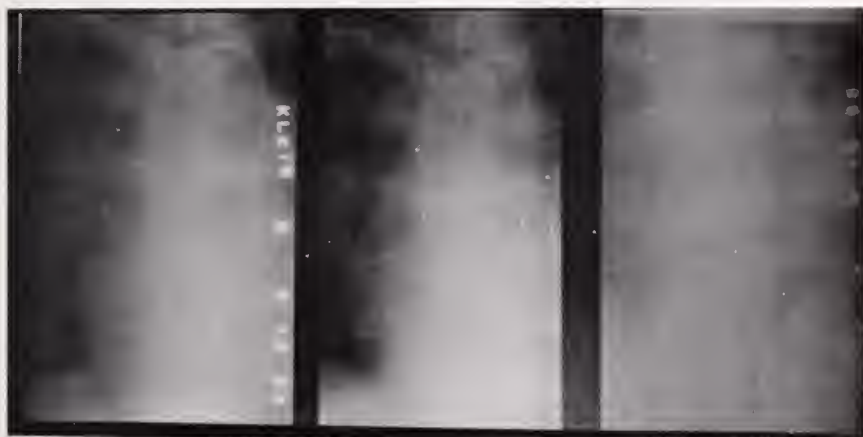


FIG. 6. (Case 3) Spot x-ray films demonstrating the sites of injection of 4 cc indigo carmine into the aorta. From left to right, the radiopaque Afford catheter is seen at the supra-aortic valve level, 2 inches above the aortic valve, and descending aorta below the arch.

The left-to-right shunt demonstrated by injection of dye at the supravulvular area of the aorta, in conjunction with the finding by oxygen determinations of a left-to-right shunt into the right ventricle, were consistent with either the rupture of an aneurysm of the sinus of



Valsalva into the right ventricle, or an interventricular septal defect of the type that occurs so high as to involve an aortic cusp and lead to aortic insufficiency. Because the diastolic murmur was a recent development, however, the former diagnosis was considered much more likely. It is known that this lesion is often associated with interventricular septal defect (4, 5) and it was postulated that both conditions might be present in his case. On a subsequent occasion, thoracic aortography and selective left ventricular angiography were performed. The existence of a shunt from the right coronary sinus of Valsalva to the right ventricle was established, but an additional interventricular septal defect could not be identified.

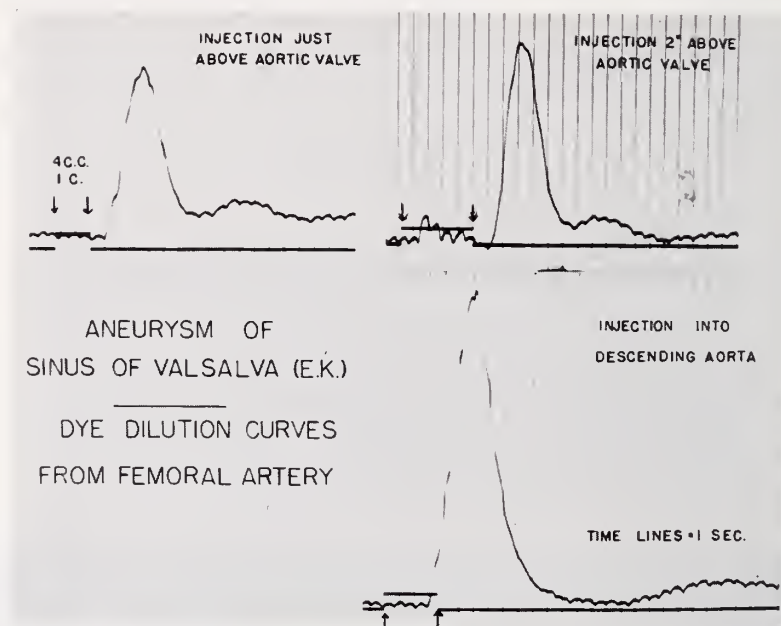


Fig. 7. (Case 3) Dye curves sampled from femoral artery after injection into three sites in the aorta. The lower amplitude of the initial curve with higher take-off of recirculation indicates that dye-containing blood is circulating through the defect when dye is injected just above the aortic valve. The slightly abnormal dye-dilution curve recorded after injection of dye at a level 2 inches distal to this, probably indicates that dye has passed backwards toward the aortic valve and hence through the defect.

#### DISCUSSION

A number of conditions produce either a continuous or machinery murmur at the base of the heart, by far the most common being a patent ductus arteriosus. Other conditions to be considered, although they are uncommon, include aortico-pulmonary window (aortic septal defect) (6, 7), ruptured sinus of Valsalva aneurysm into the right atrium, right ventricle (5, 8) or pulmonary artery (9), and interventricular septal defect with aortic insufficiency (10). Even rarer conditions which can produce a continuous murmur are bicuspid aortic valve with aortic insufficiency (11), aorta-pulmonary artery communication through the lung (12), rupture of aortic aneurysm into the pulmonary artery (13), pulmonary arteriovenous fistulae (14, 15), coronary arteriovenous fistulae (16-18) to

the right side of the heart and left ventricular wall (18) and coronary arterio-left atrial fistulae (19).

At present, patients presenting the classical clinical picture of patent ductus arteriosus are often operated upon without special studies. Some of these patients are surgically explored unnecessarily when no patent ductus arteriosus is found. In some, it is not even possible to establish the diagnosis during surgery; and in others in whom the diagnosis becomes evident on the operating table, definitive surgery may be impossible at the time. We believe that these unnecessary operations can be avoided by the utilization of the techniques previously described to establish a clear-cut diagnosis preoperatively.

Occasionally, clinical data are helpful as with the patient who develops sudden chest pain followed by shortness of breath, signs of congestive heart failure, and the first appearance of a loud continuous murmur indicating the rupture of a sinus of Valsalva aneurysm into the right side of the heart. However, in most cases with a continuous murmur, even though the clinical data may be suggestive, special studies are indicated.

As is well known, routine right heart catheterization with blood gas analysis is of value in detecting the presence of a left-to-right intracardiac or extracardiac shunt, but it cannot delineate the anatomical location of the origin of the shunt. Elevation of the oxygen values in the right ventricle suggesting a left-to-right shunt does not differentiate an interventricular septal defect with aortic insufficiency from rupture of an aortic sinus aneurysm into the right ventricle as the cause of a continuous basal murmur. Neither does elevation of oxygen values found in the pulmonary artery distinguish patent ductus arteriosus from aorticopulmonary window as a cause of the murmur.

Venous angiocardiology by and large has also proved to be of limited diagnostic value. Various adaptations of thoracic aortography involving the injection of contrast substances into the aorta or its peripheral branches have been more successful in this regard. These include injection of contrast medium through a needle after direct puncture of the ascending aorta either through the sternum, to the left of the sternum (20, 21), or by suprasternal puncture (22), into the aorta after catheterization from a peripheral artery (23, 24), through a cannula after percutaneous puncture of a common carotid artery (25), or retrograde injection through a needle after exposure of the left common carotid (26-28), or left brachial artery (29).

Brofman and Elder were the first to establish the diagnosis of "cardio-aortic" fistula by retrograde visualization when they injected 70% Diodrast through an aortic catheter and produced temporary circulatory occlusion by means of a balloon in the inferior vena cava and manual compression of the neck in order to demonstrate a tract from the right sinus of Valsalva into the right ventricle (30). In 1948, Jönsson *et al.* (24) and Burford and Carson (31) demonstrated the interarterial communication between the aorta and pulmonary artery to be a patent ductus arteriosus by injection of contrast medium into the aorta. Gasul *et al.* (32) described the first proved case of aorticopulmonary septal defect diagnosed by retrograde aortography when they injected 5 cc of 70% Diodrast

into the left axillary artery and demonstrated dye entering the pulmonary artery from the aorta just above the semilunar valves. Catheterization of the aorta with selective injection of contrast medium and rapid biplane recording of x-ray films is now extensively performed. Morrow and Braunwald employed this technique in demonstrating separate cases of aorticopulmonary window and ruptured aneurysm of the sinus of Valsalva with injection of 70% Urokon by a Gidlund syringe through a catheter placed just above the aortic valve (11).

Employing the catheter tip as a probe in the attempt to enter a communication is a technique that frequently is successful. Kjellberg *et al.* mention a case in which it was possible to advance the catheter directly from the bulb of the aorta into the right ventricle proving the existence of a communicating aortic sinus aneurysm (33). Many authors have reported the passage of the catheter from the pulmonary artery into the descending aorta, almost as the rule, in their cases of patent ductus arteriosus (34, 35). One group has been able to pass a catheter in the reverse direction (36). Dexter makes the first mention, without description of the details, of a catheter entering the aorta from the pulmonary artery through an aorticopulmonary septal defect (37). D'Heer and Nieuwenhuizen described two cases in which the course of the catheter during cardiac catheterization led to a correct interpretation of aortic septal defect (38). In one of the cases reported here, for the first time as far as we know, the catheter was directed from the aorta through an aortic septal defect into the pulmonary artery.

Differential sampling of arterial blood from brachial and femoral arteries has been of value in the diagnosis of patent ductus arteriosus with partial reversal of flow (39, 40). The unsaturated blood from the pulmonary artery is directed primarily into the lower extremities. Whatever pulmonary artery blood does reach the upper part of the body is distributed mainly to the left brachiocephalic arteries. That such findings are not pathognomonic of patent ductus arteriosus, however, is attested to by their presence in at least one reported case of aorticopulmonary septal defect where preferential flow of the right-to-left shunted blood into the descending aorta was demonstrated by simultaneous blood oxygen saturation studies from the right radial and femoral arteries (41). It is apparent that an extension of this technique to include sampling of blood from various sites in the aorta (as in our Case ~~8~~1), is capable of establishing the exact site of the right-to-left shunt.

In recent years, the application of indicator dilution curves has facilitated the detection and localization of left-to-right shunts at the base of the heart (42-44). The technique involves injection of an indicator dye into the catheterized aorta or left side of the heart and obtaining dye-dilution curves sampled from a femoral artery with a continuously recording cuvette or densitometer; or with an ear oximeter. If the dye is injected proximal to the origin of the left-to-right shunt, the smooth descending limb of the curve recorded at the femoral artery is interrupted by the delayed appearance at the sampling site of dye shunted through the pulmonary circulation. This results in a change in the slope of the curve and failure of the descending limb to reach the baseline. This occurs when

dye is injected into the aorta just above the aortic valve and is shunted through an aorticopulmonary septal defect or ruptured aneurysm of the sinus of Valsalva, or proximal to the level of the left subclavian artery when the dye is shunted through a patent ductus arteriosus. If the dye is injected distal to these sites a normal dye dilution curve is recorded.

#### SUMMARY

A group of clinically similar anomalies may be confused with uncomplicated patent ductus arteriosus and mistakenly be operated upon with that diagnosis.

Advances in diagnostic techniques and improvements in surgical therapy make it feasible as well as important that these conditions be identified prior to operation.

Three cases have been described which demonstrate the variety of methods available for diagnosis of these lesions during catheterization of the aorta.

In many respects catheterization of the aorta offers comparable diagnostic possibilities to those obtained from right heart catheterization.

#### ACKNOWLEDGMENT

Figures 3 and 7 are reproduced, with permission, from: Master, A. M. (Editor): *Visual Aids in Cardologic Diagnosis and Treatment*, New York, Grune & Stratton, 1960.

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## SUSCEPTIBILITY OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI TO HETEROLOGOUS ANTIBIOTICS\*

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In the course of an investigation into the biological, biochemical, and immunological characteristics of staphylococci in relation to their pathogenicity, a series of one hundred hospital staphylococcal strains isolated from clinical specimens during late 1959 and early 1960, were tested for their susceptibility *in vitro* to a variety of antimicrobial agents by means of the tube dilution method. Analysis of these data provided an opportunity to determine the relative susceptibility of strains found resistant to each antibiotic to the gamut of heterologous antibiotics. Information thus provided may prove of value in indicating the potential effectiveness of alternative antibiotics when a favorable response fails to be elicited by certain antibiotics.

The strains employed in this study were isolated from a number of different clinical lesions and sources (Table I). They represent a wide range of actual or potential pathogenicity as evidenced by their origin and their possession or lack of possession of certain biochemical or biological characteristics presumptive of virulence. Eighty were of the pigmented variety; 85 fermented mannitol; 73 produced coagulase and 74 alpha hemolysin; and 76 were pathogenic to mice with the aid of Triton-X as an adjuvant when injected intraperitoneally (1). Based upon these criteria, approximately  $\frac{3}{4}$  of the strains were of the "pathogenic" type. Nineteen strains were lysed by 80/81 and one by 52A/79 bacteriophage types exclusively, 52 by a variety of phage types and 28 were not lysed by any of 24 standard phage types. However, to date no distinct correlation has been established between staphylococcal pathogenicity (2, 3), or of phage type (3-5) and range of antibiotic susceptibility except with strains of the 80/81 phage type which are resistant to the action of penicillin or tetracycline with but rare exception.

### METHOD

The tube dilution method was the procedure employed to test antibiotic susceptibility. Composition of the assay medium, preparation of standard antibiotic solutions and dilutions, age and size of the bacterial inocula of the various test strains, as well as temperature and duration of incubation, all of which exert an influence upon the outcome of sensitivity determinations, were all carefully standardized. The medium employed, Trypticase Soy Broth (BBL), is one that promotes rapid bacterial multiplication. Tests were performed in 2 ml

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\* This investigation was supported by Research Grant E-2937 of the U.S. Public Health Service, National Institutes of Health.

amounts by the addition of 1.9 ml of an overnight broth culture of each strain, diluted  $10^{-3}$ , to varying concentrations of standard antibiotic contained in 0.1 ml of assay medium. Tubes were incubated for 18 hours at  $37^{\circ}\text{C}$  after which the minimum concentration of antibiotic resulting in complete visual inhibition of the standardized inoculum of each strain under study was noted. A growth control tube containing the same bacterial inoculum without antibiotic was used with each determination. Because some of the components of the culture medium are capable of interfering with the activity of certain antibiotics, for example with bacitracin, neomycin and streptomycin, a dilute broth containing 3 parts of the above medium and 5 parts sterile distilled water was employed in order to eliminate or minimize such potential interference whenever strains were tested against these antimicrobial agents. Test bacterial strains grew readily and rapidly in this dilute medium.

TABLE I

*Origin of 100 Test Hospital Staphylococcal Strains*

Source	Number
Nose and throat . . . . .	31
Purulent exudate . . . . .	28
Urine . . . . .	18
Skin . . . . .	8
Stool . . . . .	4
Blood . . . . .	3
Sputum . . . . .	3
Eye . . . . .	2
Pleural fluid . . . . .	1
Umbilicus . . . . .	1
Vagina . . . . .	1
Total . . . . .	100

## RESULTS

The percentage of strains found sensitive to each of the antibiotics investigated is contained in Table II. Inhibition by antibiotic concentrations equivalent to attainable blood levels rather than by an arbitrarily selected amount was the criterion employed for classifying strains as being *Sensitive* to a particular antibiotic. Strains inhibited by bacitracin, erythromycin, oleandomycin, tetracycline— $5\text{ }\mu\text{g}$  per ml; penicillin—10 units per ml; chloramphenicol, ristocetin and vancomycin— $15\text{ }\mu\text{g}$  per ml; and neomycin, novobiocin, streptomycin— $20\text{ }\mu\text{g}$  per ml were designated as *Sensitive*. Organisms requiring amounts greater than the above to effect their inhibition, were classified as *Resistant*. Thus, a strain inhibited by  $10\text{ }\mu\text{g}$  per ml of tetracycline and by the same concentration of chloramphenicol, was classified as *Resistant* to the former but *Sensitive* to the latter, although susceptible to the same amount of both antibiotics, since



the above level is readily achievable with chloramphenicol but not with tetracycline.

The ratio of *Sensitive* strains to each antibiotic contained in the table does not necessarily reflect general incidence of antibiotic susceptibility since the test

TABLE II  
*Antibiotic Susceptibility of 100 Test Staphylococcal Strains*

Antibiotic	Number of Sensitive Strains
Bacitracin . . . . .	77
Chloramphenicol . . . . .	67
Erythromycin . . . . .	57
Neomycin . . . . .	100
Novobiocin . . . . .	86
Oleandomycin . . . . .	64
Penicillin . . . . .	31
Ristocetin . . . . .	100
Streptomycin . . . . .	42
Tetracycline . . . . .	43
Vancomycin . . . . .	100

TABLE III  
*Proportion of Antibiotic Resistant Staphylococcal Strains Susceptible to Each Heterologous Antibiotic\**

Antibiotic	Total Resistant Strains	Number Sensitive to:							
		Baci-tracin	Chlor-am-phenicol	Eryth-romycin	Novo-biocin	Oleand-omy-cin	Peni-cillin	Strepto-mycin	Tetra-cycline
Bacitracin . . . . .	23	—	14	13	22	12	6	9	10
Chloramphenicol . . . . .	33	26	—	4	24	9	2	2	1
Erythromycin . . . . .	43	33	16	—	29	8	2	0	0
Novobiocin . . . . .	14	13	5	0	—	1	1	0	0
Oleandomycin . . . . .	36	25	13	3	23	—	2	0	0
Penicillin . . . . .	69	52	38	28	56	34	—	15	19
Streptomycin . . . . .	58	44	27	15	44	22	4	—	6
Tetracycline . . . . .	57	44	25	14	44	20	7	5	—

\* All antibiotic resistant strains were susceptible to the action of neomycin, ristocetin and vancomycin.

strains were especially chosen to include a broad sample of hospital staphylococci isolated from different clinical lesions and sources and of varied biochemical and biological characteristics.

A varying proportion of strains resistant to each antibiotic were sensitive to other antibiotics. As may be noted in Table III, cross resistance between antibiotics varied considerably. Cross resistance between bacitracin and novobiocin was minimal since 22 of the 23 bacitracin resistant strains were sensitive to

novobiocin and of the 14 novobiocin refractory strains, 13 were susceptible to bacitracin. A large proportion of the chloramphenicol resistant strains were sensitive to bacitracin and to novobiocin but relatively few to the remaining heterologous antibiotics. Cross resistance was marked between erythromycin and oleandomycin since strains resistant to one were generally resistant to the other

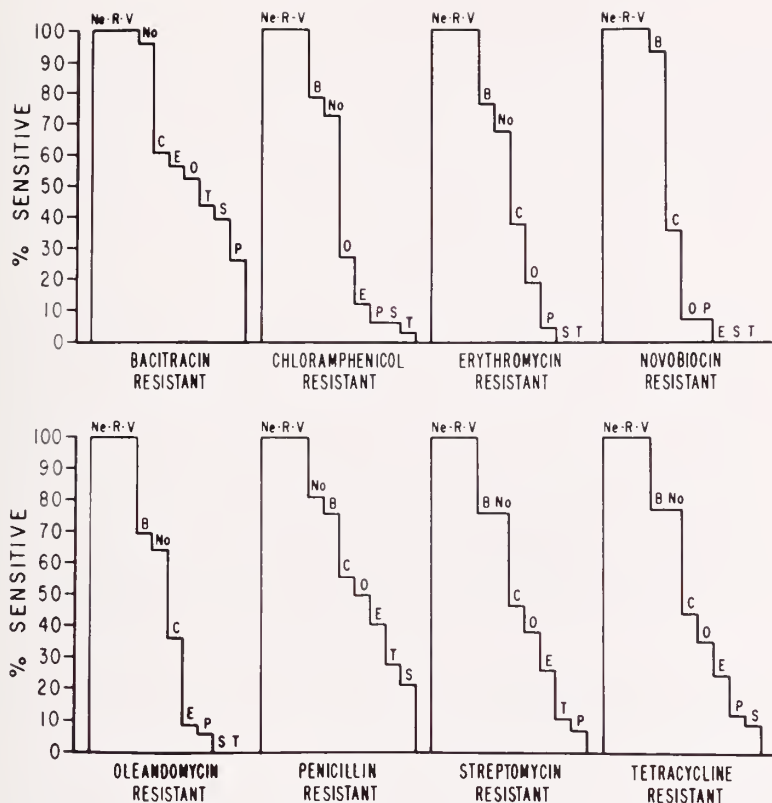


FIG. 1. Relative percentage of antibiotic resistant strains sensitive to each heterologous antibiotic:

Ne	Neomycin	E	Erythromycin
R	Ristocetin	O	Oleandomycin
B	Bacitracin	T	Tetracycline
V	Vancomycin	S	Streptomycin
No	Novobiocin	P	Penicillin
C	Chloramphenicol		

and vice versa. On the other hand, a good number of the 43 erythromycin and 36 oleandomycin resistant strains proved susceptible to bacitracin and novobiocin, a smaller number to chloramphenicol and only 2 strains of each were sensitive to penicillin and none to streptomycin or tetracycline. Cross resistance between novobiocin and the other antibiotics besides bacitracin proved moderate with chloramphenicol but marked with erythromycin, streptomycin, tetracycline, oleandomycin and penicillin since the 14 novobiocin resistant strains were

all resistant to the first three and only one novobiocin resistant strain was sensitive to each of the last two agents. Susceptibility of penicillin, streptomycin and tetracycline resistant strains to other antibiotics varied considerably, the largest proportion being sensitive to novobiocin or bacitracin and then to chloramphenicol, oleandomycin, erythromycin, tetracycline, penicillin, and streptomycin generally in the order named.

The comparative efficacy of each heterologous antibiotic against strains refractory to each antibiotic specifically, as evidenced by the relative percentage of strains of the latter that proved sensitive to alternative antibiotics, is depicted graphically in Fig. 1. As may be observed from the graph, optimal results in the secondary treatment of initially refractory staphylococcal infections may be anticipated with neomycin, ristocetin or vancomycin, then novobiocin or bacitracin, followed by chloramphenicol, oleandomycin or erythromycin and finally with tetracycline, penicillin or streptomycin.

#### SUMMARY

One hundred hospital staphylococcal strains from a number of different sources with assorted biochemical and biological characteristics were tested for their *in vitro* susceptibility to a variety of antimicrobial agents by means of the tube dilution method. Proportion of resistant strains to each antibiotic that were sensitive to other heterologous agents was determined. All strains regardless of their resistance to any particular antibiotic were sensitive to neomycin, ristocetin and vancomycin; a good proportion to bacitracin and novobiocin, next to chloramphenicol, oleandomycin and erythromycin to a lesser extent, and relatively few to tetracycline, streptomycin or penicillin.

#### ACKNOWLEDGMENTS

We are greatly indebted to Michaela Modan, Dalia Maor and Otto Krauthamer for their very capable technical assistance.

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# *Clinico-Pathological Conference*

## PYELONEPHRITIS WITH NEPHROSIS

*Edited by*

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A 51 year old Negro female was admitted to The Mount Sinai Hospital complaining of swelling of the ankles for four months. This began insidiously and would subside during the night. Some periorbital edema was also noted. The patient stated that she had mild dyspnea on exertion, cramps in her legs at night, nocturia, and poor appetite. No pain, headache, dysuria or cloudy urine had been noted.

She had a swollen gland in her neck removed at age 13, a myomectomy at 37 and a hysterectomy at 42. Following this she had x-ray and radium therapy because of pelvic pain and dyspareunia. She was born in New York, worked with dyes for fifteen years, had been a heavy drinker, and smoked a pack of cigarettes a day. Her mother died at 59 of heart disease and her father at 85 of asthma.

She appeared thin and chronically ill and had some facial edema. She was afebrile. She had bilateral corneal opacification. A 1.5 cm mass was felt in the left lobe of the thyroid. The neck veins were not distended. The lungs were clear, the heart was not enlarged, the pulse was normal and the blood pressure was 130/72. A harsh grade II apical systolic murmur was heard. No organs were felt in the abdomen; pelvic examination revealed no uterus or masses, and rectal examination was negative. Ankle, pretibial, and sacral edema were present. Neurological examination was normal.

The pertinent laboratory data are summarized in Table I. The sedimentation rate was 84 mm/hr, differential counts, tests reflecting hepatic function, stool examinations, serology, lupus preparations, platelet counts, bleeding and clotting time, ASLO titer, urine cultures, bone marrow, chest x-rays and ECGs were all normal.  $I^{131}$  uptake in 24 hours was 47% and the blood iodine level was 4.38 mg%. Serum electrophoresis showed very low albumin, markedly increased alpha-globulin and slightly reduced gamma globulin. Urinary excretion of 17-ketosteroids was 2.67 mg/24 hours and 11-hydroxysteroids 4.2 mg. Urine protein excretion varied from 6.5 Gm to 8.3 Gm in 24 hours. The patient was unable to concentrate her urine beyond 1.006 on a concentration test. Venous pressure was 30 cm and circulation time with Decholin was 14 seconds. On a Congo red test 55 per cent of the injected dye was retained and some was seen in the urine. X-rays of the neck showed irregular calcifications on both sides and films of the abdomen showed a calcified node in the right pelvis. RPP  $\times 2$  was negative. Tongue and gum biopsies were negative for amyloid.

The patient was afebrile throughout her hospital stay but showed a marked decline in hemoglobin to a low of 5.8 Gm. Along with this the BUN rose, she had

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massive anasarca, and vomited a great deal. She was treated with blood, a low salt and protein diet, calcium, chlorpromazine, Furadantin, Medrol, isoniazid, and Amphogel, none for long periods of time. A kidney biopsy was not done because the right renal shadow was not discernible. After two months in the hospital she began to improve and lost most of her edema fluid. On the 87th hospital day she was discharged.

While at home she was in bed and comfortable for two weeks. She then became weak and lethargic and her urinary output dropped. She had headaches, epi-

TABLE I  
*Laboratory Data*

	1st admission 10/18	2nd week 10/30	2nd month	2nd admission 2/13	Terminally 5/15
Urine spec. gravity.....	1015		1002	1007	1002
reaction.....	acid	acid	alk.	acid	acid
albumin.....	4+	4+	3+	3+	3+
erythrocytes.....	4-5	2-4	0-2	0	10-12
leucocytes.....	20-30	many	2-3	packed	many
casts.....	hyal. gran.	gran.	0	0	0
	WBC				
Hemoglobin (Gm%).....	13.6	13.0	7.8	8.0	5.4
WBC (/mm <sup>3</sup> ).....	7800	8400	14050	16000	
BUN (mg%).....	55	75	51	102	142
Glucose (mg%).....	44	70		91	100
CO <sub>2</sub> (mEq/l).....		15.0	18.3	8.9	8.3
Chlorides (mEq/l).....		105	112	108	112
Albumin/globulin (Gm%).....	1.9/3.4	1.6/3.3	2.1/2.0	2.4/2.8	
Ca (mg%).....		5.1	7.4	5.2	
P (mg%).....	5.6	7.2	6.0	8.4	
K (mEq/l).....		4.3	4.0	4.4	6.0
Na (mEq/l).....		133	142	140	133
Cholesterol (mg%).....	358	366		220	220
Alk. phosphatase (KAU).....	10.4	10.3			
Creatinine (mg%).....		7.8	5.9	15.8	16.0
Uric acid (mg%).....	6.2	7.2	6.7	12.6	

gastric pain, anorexia and vomiting. Exactly one month after discharge she had a convulsion, lost consciousness and was readmitted.

Her temperature was 100.2°F., pulse 90/min. and blood pressure 160/95. She had a uriferous odor and was very edematous and lethargic. She had a positive Chvostek sign. The findings were otherwise as on the first admission.

Laboratory data are summarized in Table I. Spinal fluid pressure and examination were negative. Sick cell preparations were 2% positive and hemoglobin electrophoresis showed a small amount of S with otherwise only A hemoglobin. Urine cultures were again negative. Urine protein was 6.55 Gm/l, urinary sodium 75 mEq/l, potassium 19 mEq/l, and chloride 68 mEq/l on admission and one month later sodium and potassium were both 41 mEq/l. Venous pressure

was 60 mm and the circulation time was 25 seconds. Chest x-rays showed blunting of the costophrenic sinuses which had been noted earlier and some increase in the size of the heart.

The patient had one seizure immediately after admission during which her blood pressure rose to 170/100 and then promptly fell to normal. After a week of semiconsciousness the patient became alert and her urinary output rose while her BUN fell. She vomited a great deal during the entire hospital stay. She was given fluids, blood, antibiotics, vitamins, promazine and Amphogel, and she improved for about two months. Her blood pressure was normal (110-130) systolic, 70-80 diastolic) but her hemoglobin dropped to as low as 5.6 Gm requiring frequent transfusion. On the 70th hospital day a precordial friction rub was heard. This disappeared after a week but the patient began to vomit and she became lethargic again. On the 83rd hospital day she began having seizures and after a week of repeated seizures, she expired on the 99th day of her second admission, about 11 months after the onset of her symptoms.

*Dr. Marvin Levitt\**: I have always felt that it is dangerous to be vulnerable to the pathologists. It is an awkward position for a physiologist.

In essence, we have a woman with a very conspicuous nephrotic syndrome and large albumin loss despite markedly reduced kidney function. This patient revealed a malignant nephrotic syndrome which lasted about eleven months from the time of the onset until her demise. Despite the development of marked renal failure, it was not associated with any conspicuous increase in blood pressure.

I think we can approach a diagnosis on the basis of the laboratory data. The original hemoglobin is of some importance. Nephrotics tend to have remarkably good hemoglobin concentrations for their degree of protein wasting. We would not expect a woman as sick as this, who came into the hospital with blood urea of 55 mg%, to have a hemoglobin of almost 14 Gm%. This persistence of relatively good hemoglobin concentration probably results from the marked degree of hypoproteinemia. I suspect that the normal hemoglobin was a reflection of the reduced circulating volume which characterizes hypoproteinemia. This reduced circulating volume is of extreme importance because it explains the vulnerability of the nephrotic to any further ill effects of depletion of circulating fluid volume. Other than that, the laboratory data show that she had a very low serum calcium concentration which in large part is probably an expression of the marked hypoproteinemia with failure of the protein to bind calcium. Cholesterol concentration was considerably elevated but perhaps a little less so than one would expect with this degree of nephrotic syndrome. It began to fall terminally. She had considerable renal failure at her first admission with a serum creatinine of almost 8 mg%. She did have a transient improvement in renal function in association with some diuresis although weights are not given in the protocol. Marked hyposthenuria was present in association with severe renal failure. Despite the presence of albumin, red cells, white cells, and casts in the urine on many occasions, I do not see any report of lipid bodies. I do not

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think that this finding would be of any further help because we have already convincing evidence that she had a nephrotic syndrome. Serum electrolyte concentrations were those of serum dilution and severe acidosis due to the renal failure but these are not specific findings. Interestingly, as her renal function did deteriorate, a slight but distinct increase in the level of the serum albumin appeared. The laboratory data do not help us to distinguish between the varied forms of nephrosis or nephrotic syndrome this patient may have had. I am particularly interested in the size of the kidneys and whether they can be seen on x-ray.

*Dr. Sigmund A. Brahms\**: First, the film of the neck showed a series of discrete calcifications on each side and these were apparently calcifications in lymph nodes. We heard the story which referred to disease in the cervical lymph nodes at the age of thirteen.

The chest films showed some thickening of the pleura in both apices. This is consistent with old tuberculosis and it is something which we see frequently in this part of the country in adults. No infiltration was seen in either lung. In a film made shortly after the first admission, there was some haziness in the costophrenic sinuses. The heart was not enlarged and there were calcifications in the aortic arch. During the last part of the course, there was very little change in the appearance of the heart and lungs. There was some increase in the size of the heart shadow apparently at the time when a precordial friction rub was heard and the possibility of a small pericardial effusion could be suggested, especially upon comparison with the other films. In this same film there was a little blunting of the left costophrenic sinus.

The abdomen films showed the following: The left kidney was small. The right kidney was not definitely identified. There was some calcification in the lower abdomen in the lymph nodes. There was no distinct distention of any part of the bowel and no haziness in the pelvis which may be related to previous surgery. In a film made near the end of the course, there was little change. There was an overall haziness, a little gas and some short segments of small bowel and adjacent loops separated slightly, an appearance suggesting an increase in the quantity of peritoneal fluid. At no time in the series of films of the abdomen did we see evidence of the enlargement of the liver or spleen.

*Dr. Levitt*: Was there anything to suggest something in the pelvis pushing the bowel up? This woman had a procedure eight years ago and was given radium therapy. We do not know the nature of this pathologic process.

*Dr. Brahms*: I saw a little gas in the rectum and the haziness which I described. I do not know exactly what its significance is.

*Dr. Levitt*: I think that this patient may be summarized as one with a malignant nephrotic syndrome associated with rapid appearance of renal failure and demise in a brief period of time, a failure to respond to any form of therapy and the absence of any considerable increase in blood pressure.

When I first saw this woman on the wards, I was struck with the possibility

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that she might have amyloid disease of the kidneys. I still think this is a very good possibility, namely, amyloid nephrosis causing an extensive nephrotic syndrome, failing to respond to any therapy and causing a rapidly moving and malignant nephrosis without elevation of the blood pressure. The somewhat decreased rate of 17-ketosteroid excretion would be consistent with the possibility of adrenal amyloid as would the normal blood pressure.

We have a little trouble in establishing the diagnosis of amyloid. The Congo red test was normal. The liver was not enlarged, although the absence of a large liver does not rule out renal amyloidosis. The diagnosis was not established on biopsy of the tongue and gums which, again does not rule out the presence of renal amyloid. What I am most unhappy about is that I do not have any etiological explanation for the presence of secondary amyloidosis, although it is possible that this woman had a retroperitoneal tumor related to her old cervical lesion. Any malignancy can predispose to the development of a secondary type of amyloidosis.

I have seen one nephrotic patient who died of severe amyloid nephrosis which had no etiological explanation. Therefore, the possibility that this was an amyloid nephrosis secondary to a retroperitoneal tumor or other tumor causing a rapidly progressing nephrotic syndrome with renal failure not responding to any therapy is a reasonable hypothesis. This would even be consistent with the fact that the left kidney is smaller than expected in most amyloid nephrosis since in time the amyloid kidney may become contracted.

The possibility of this disease being ordinary glomerulonephritis of the membranous and proliferative type must be considered. I must admit that the clinical course was a little too quick to satisfy me although I have seen nephrotics run down very quickly. I have my doubts whether Dr. Popper would choose an ordinary glomerulonephritis for a CPC, first, and secondly, the course is too quick, a little too malignant. Furthermore, the absence of hypertension in the presence of renal failure is a fact I find hard to associate with chronic glomerulonephritis.

The procedure she underwent nine years ago, I think, may be of extreme relevance. It is an old observation that any sustained increment in renal venous pressure will ultimately produce a nephrotic syndrome. There was the famous British runner who damaged his inferior vena cava in the course of a 100 yard dash who lived 25 years with a nephrotic syndrome as a consequence of the renal congestion.

Thus, it is conceivable that this woman had a carcinoma of the cervix which recurred and spread retroperitoneally involving both renal veins. The nephrotic syndrome would then be a consequence of this increase in renal venous pressure. The interesting thing about the nephrotic syndrome of renal vein thrombosis is that it is an extrapolated physiological form of orthostatic albuminuria. It takes place in someone who assumes a lordotic position and increases the renal venous pressure. If the patient had renal vein thrombosis, it may have been partial at first and later became complete. It is further possible that this mechanism could have produced a considerable venous stasis with an alteration of



the basement membrane of the glomerulus which ultimately led to the nephrotic syndrome. I have not seen nor has there been described a nephrotic syndrome due to metastatic cervical carcinoma, but I think it is something of which one must think. I put this second as an etiological possibility.

The frequency with which lupus nephrotic syndrome and nephritis are associated with a relatively modest increase in serum cholesterol has been emphasized. It would be hard for me to imagine that at The Mount Sinai Hospital, lupus with a nephrotic syndrome would be overlooked. Certainly the terminal pericarditis could have been uremic. There was no evidence of fever, joint symptoms or rash. Although it is possible, I find it hard to believe that a lupus glomerulonephritis was overlooked.

I come back again to the most likely diagnosis, namely, an amyloid kidney, possibly a consequence of retroperitoneal tumor. I am still quite concerned with the possibility of retroperitoneal obstruction to the renal veins producing a nephrotic syndrome as a consequence of renal vein thrombosis. The nephrotic syndrome can be seen in diabetes. There is no evidence here for diabetes. Nephrosis in severe nephrosclerosis has been described but we had no reason to suspect that. The patient was not hypertensive and there was no reason to believe there was extensive nephrosclerosis. I have seen nephrotic syndrome described in any disease in which the renal vein pressure increases, such as severe constrictive pericarditis. I find it hard to delineate any evidence for pericarditis in this woman or restricted type of increased venous pressure. We have talked of nephrosis as a consequence of drugs. It has been described with antiepileptic drugs. It has been as a consequence of periarteritis. We have not seen this here.

After considering many of the etiological possibilities, I still feel that in this rapidly moving malignant nephrotic syndrome, its failure to respond to steroids and the absence of an elevated blood pressure, amyloid nephrosis would be a reasonable diagnosis. A similar picture could be explained by a recurrence of retroperitoneal tumor with obstruction of the inferior vena cava and obstruction of the renal venous blood supply.

*Dr. Hans Popper\**: At the autopsy there was ankle edema and an accumulation of some 2,000 ml of fluid in both pleural cavities. In view of the convulsion we were interested to demonstrate abnormal changes in the brain, but the gross examination was entirely normal and not even sclerotic changes were seen. Microscopic examination also failed to reveal any significant changes.

The thyroid showed some calcifications in colloid containing nodules, of little interest in the present problem.

The lungs were emphysematous and contained a moderate amount of edema fluid. No recent tuberculosis was found although apical scarring was present.

The heart was of normal size and weight and slightly dilated. There was a slight irregularity over the epicardial surface but we failed to see any acute pericarditis. Rather, it was a chronic low grade calcifying infiltration, possibly related to the uremia which has been well-established on a biochemical basis.

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The trabeculae carneae were very delicate and small. While there was dilatation, hypertrophy was absent. The heart muscle was dark brown in color. On microscopic examination lipofuscin pigment was seen in heart muscle fibers, indicative of atrophic changes. More intensive examination showed interstitial myocarditis in a few places, subacute in nature, with relatively little destruction of myocardial fibers. This possibly was a reflection of the electrolyte imbalance and could have accounted for the cardiac decompensation reflected in the elevated venous pressure and the prolongation of the circulation time.

The spleen was small and atrophic and had follicles in the pulp. The white pulp was literally loaded with iron pigment. There was severe reticuloendothelial hemosiderosis, also found in the lymph nodes. This was related to a combination of factors, mainly anemia and blood transfusions. In the bones we saw a significant amount of osteoporosis indicated by the very delicate structure of the bony trabeculi. The marrow showed some increase in reticulum cells with somewhat reduced hematopoiesis. Marrow reticuloendothelial cells contained a large amount of iron. In addition, there was considerable recent absorption of bony trabeculi associated in part with fiber formation. This was not fully developed osteofibrosis but the early changes probably indicate prolonged acidosis. Both these features of hemosiderosis and osteofibrosis were apparently renal in origin against the background of the history but were somewhat at odds with this story in that they pointed to a somewhat longer duration of the renal insufficiency than the 11 months which is in the record.

The liver was of normal size, weighing 1250 Gm. It was brown in color and had several violin string adhesions between the diaphragm and its convex surface. We do not know the etiology of this circumscribed, long-healed, fibrous peritonitis but pathologists are always inclined, maybe in a mean vein, to assume that it resulted from a gonorrheal infection originating in a fallopian tube. The liver had a normal architecture with a borderline increase of the portal connective tissue, not too much congestion but again reticuloendothelial hemosiderosis. The liver cells were virtually free of iron in contrast to parenchymal hemosiderosis. I saw true hemochromatosis only once associated with anemia of chronic glomerulonephritis. In most instances, the iron reflects anemia and blood transfusions and perhaps something related to a chronic prolonged depression of hematopoiesis.

The pancreas showed atrophy. The acini were small and we saw inspissated material in the lumens of the atrophic acini. This occurs because of dehydration in this stage of uremia. Despite this uremic manifestation, there was no uremic gastritis, enteritis or colitis.

The urinary bladder was fairly normal being small and contracted with a fairly normal epithelium. There was no tumor in the pelvis and apparently nine years before death, the genital organs, namely, uterus, ovaries and tubes, had been removed. There was no tumor retroperitoneally in this area. The adrenals were small as suggested by the low ketosteroid excretion.

The most remarkable feature was the small kidneys. The left one weighed 44 Gm and the right 49 Gm (Fig. 1). They were only three centimeters in di-

ameter. They were small, shrunken, pale, and homogeneous appearing with irregular scars throughout. The renal pelvis was somewhat thickened. The first thought was that of a chronic glomerulonephritis. On the outer surface of the kidney there was some irregular scarring and depressions going somewhat deeper. On the cut surface extensive scarring was noted around the pelvis with a small and shrunken cortex and an irregular and somewhat deformed medullary portion. Microscopically, the architecture was virtually abolished. Cellular infiltration, large cystic and dilated tubules, and a few glomerular scars were seen (Fig. 2). Up to this point the kidney was a contracted kidney of Bright's disease without any evidence of its etiology. This was the end stage of a contracted kidney somewhat peculiar to the clinical picture in this case. The dilated tubules contained inspissated material and resembled a colloid goiter (Fig. 3). This concentrated tubular content in dilated tubules results from distal nephron ob-

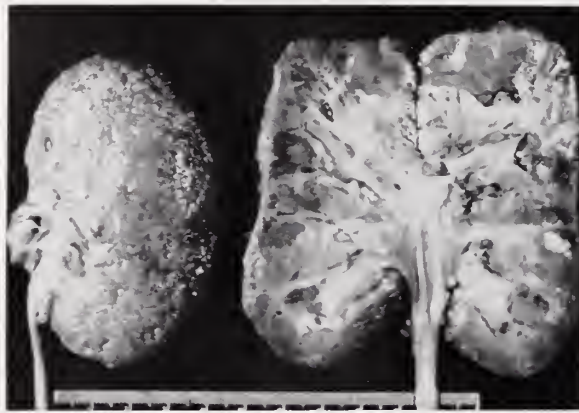


Fig. 1. Photograph of the kidneys showing contracted organs with a granular surface.

struction, for instance, in a chronic pyelonephritis. We had a pyelonephritic contracted kidney before us. We turned to the area of the renal pelvis and saw a large amount of scarring and chronic interstitial peripelvic infiltration, both pyelonephritic manifestations. The scar tissue extended from the medullary portion into the cortical portion. In the cortex there was irregular scarring, fibrosis, severe interstitial infiltration, and periglomerular scarring. The scarred glomeruli were bunched together, a characteristic of the pyelonephrotic contracted kidney.

The renal vessels showed relatively little significant vascular changes. The arteries were somewhat tortuous with some intimal proliferation (Fig. 4). The arterioles showed a little fat but no other changes. This was the type of the chronic pyelonephritic kidney that had been separated from the more typical chronic nephritis. Clinical manifestations were identical in most cases although normal blood pressure was sometimes found. The tubules in many places were atrophic, probably due to the disturbed glomerular function. The atrophic tubules were surrounded by many inflammatory cells, probably as a reaction to the destruction of the tubular epithelium.



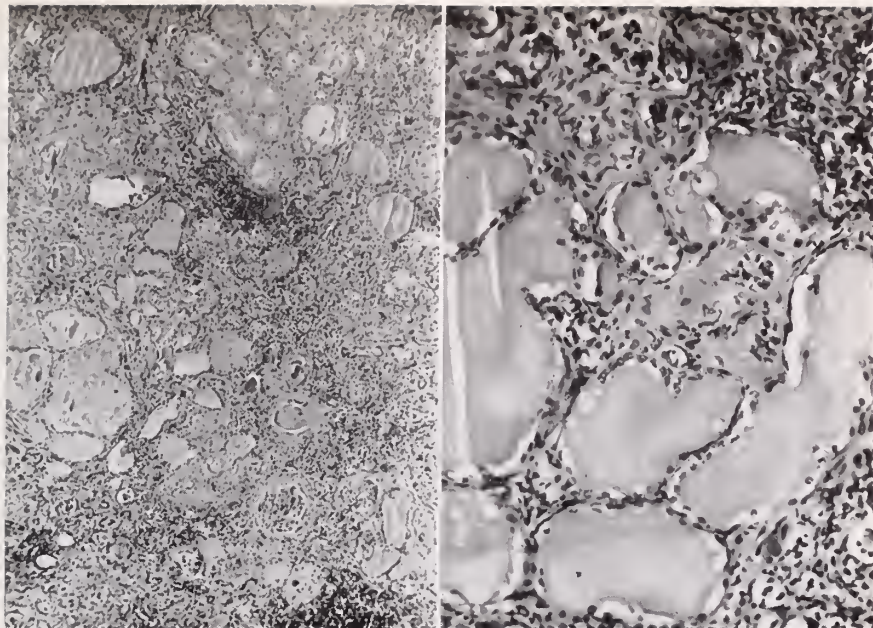


FIG. 2. Section of renal cortex in which the architecture is destroyed. Tubules are cystically dilated, interstitial infiltration is present and glomeruli are scarred, all suggesting pyelonephritis (H & E  $\times 44$ ).

FIG. 3. Thyroid-like appearance of renal tubules with inspissation of contents (H & E  $\times 120$ ).

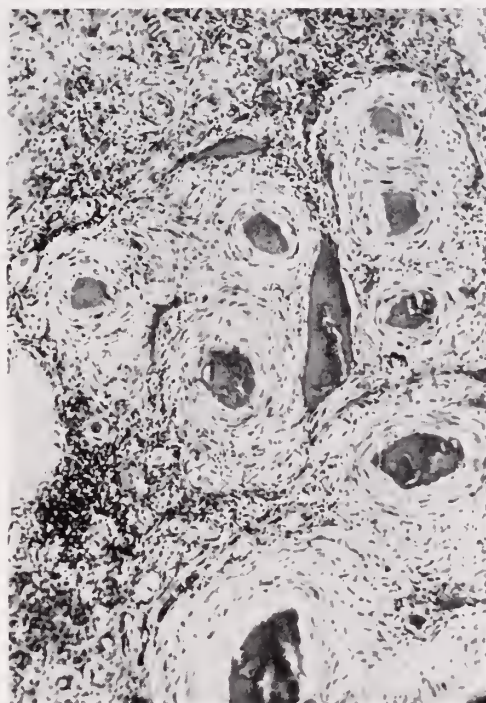


FIG. 4. Larger renal arteries with thickening of the intima (H & E  $\times 120$ ).



I have presented the classical picture of chronic pyelonephritic kidney with pyelonephritic contracted kidney which has been called by some pyelonephritis lenta. Everything fits into this background except the history. Dr. Levitt will probably tell me we mixed the case up in the pathology department and wishes now for me to present something that correlates better with the elegant clinical discussion he presented. Let us look further to see whether we can find something which puts the two aspects together. We did find evidence of acute pyelitis focally. Dr. Levitt pointed out that one should have examined the urine for lipid. I could not do that, but I could show the fat in the tubules (Fig. 5). Some glo-

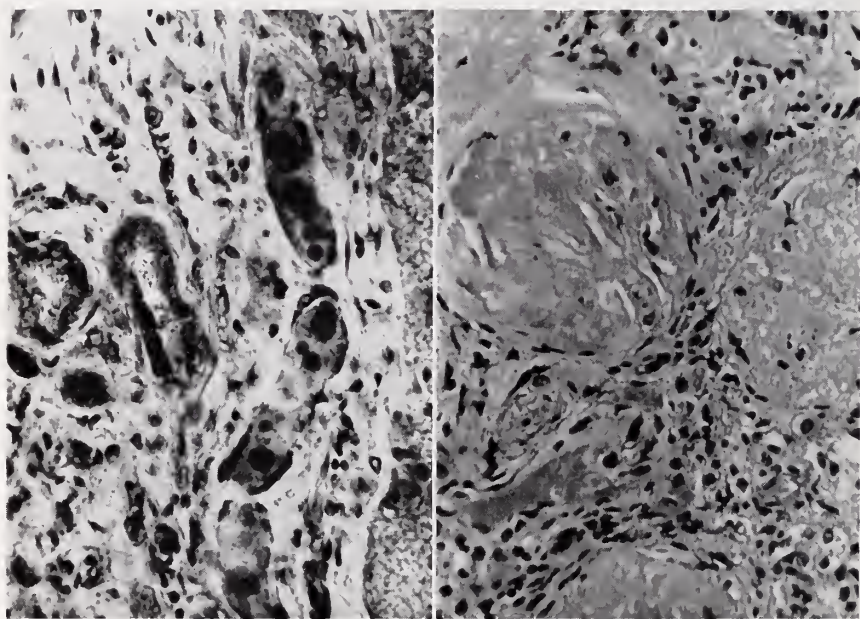


FIG. 5. Fat droplets in the lumens of tubules suggesting glomerular disease (Oil red O—H & E  $\times 120$ ).

FIG. 6. Complete obsolescence (scarring) of glomeruli (H & E  $\times 120$ ).

meruli had adhesions and in some the glomerular loops appeared lobulated. Material in these glomeruli which were large, broadened the basement membrane. Cells disappeared gradually in other areas, leaving what looked like a glomerular scar (Fig. 6) except that it did not consist of scar tissue. In the obliterated glomerulus there were no fibers and no sclerosing of the glomerulus (1, 2). It was the result of tremendous protein seepage around the entire glomerular loop with a few cells remaining between loops. The process started in the epithelial cells which became separated by protein (Fig. 7). This protein filled the entire basement membrane which eventually became thickened (Fig. 8) (3). This was the classical picture of a nephrosis in the sense of a subacute membranous glomerulonephrosis.

Let us put together the changes we have seen. The first lesion was a colloid

nodular goiter. Perihepatic violin string adhesions were present. A hysterectomy and salpingo-oophorectomy were done nine years before death and perhaps this is when pyelonephritis developed. This pyelonephritis apparently progressed to the pyelonephritic contracted kidney with the characteristic changes of peripelvic scarring and internal hydronephrosis, periglomerular scarring, glomerular bunching and intimal thickening of arteries with normal arterioles and normal blood pressure. This apparently occurred because the tubules were completely destroyed and were not able to form the so-called tubular pressor substance.

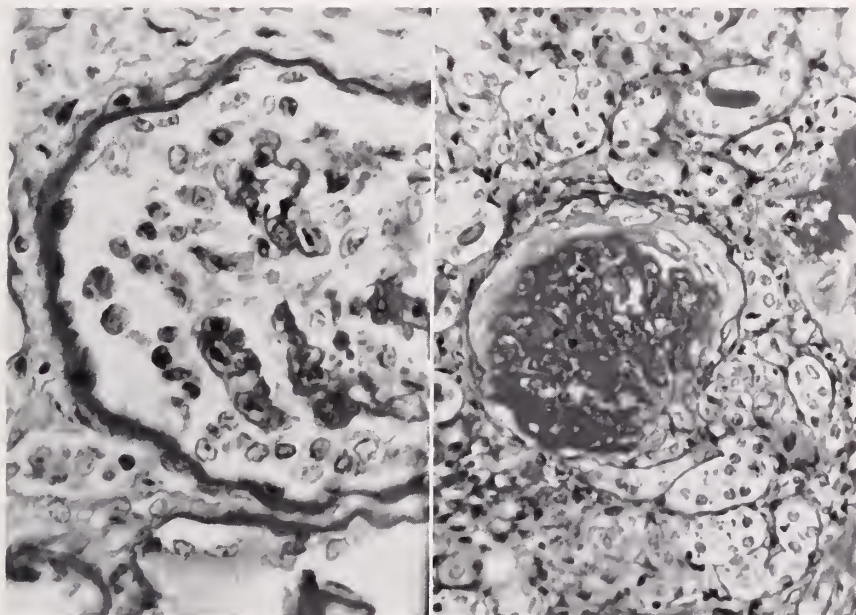


FIG. 7. Droplets of carbohydrate containing protein in epithelial cells of the glomerulus and beginning deposition of similar material in the basement membrane (PAS  $\times 440$ ).

FIG. 8. Scarring and obsolescence of glomeruli due to collapse of protein soaked membrane without fibrosis. The periglomerular fibers show no inhibition of the carbohydrate-protein (PAS  $\times 120$ ).

There was reticuloendothelial hemosiderosis, severe anemia, and osteoporosis. This pyelonephritic contracted kidney showed spotty acute pyelonephritis. This must have occurred episodically accounting for the red cells and leukocytes which had been found in the urine. However, she completely independently developed a subacute membranous glomerulonephritis. There was no evidence in this case that typical streptococcus strains were involved with production of antigen-antibody reactions and antistreptolysin titers (4). I do not know the etiology of the lesion but at least it leads to glomerular obsolescence with edema, hypercholesterolemia, and lowered serum protein. Finally, the combination of the pyelonephritic contracted kidney and nephrosis led to uremia with vomiting, lethargy, convulsions, and pericarditis.

*Dr. Levitt:* I was quite anxious until you found the membranous glomerulonephritis, Dr. Popper, because with all the etiological factors that have been implicated in the development of a nephrotic syndrome, the one which is still to be proved is pyelonephritis.

*Dr. Popper:* I think there might be two independent diseases in this case.

*Dr. Levitt:* I think you are right and I think in terms of your hypothesis, it is reasonable that the underlying renal disease made her vulnerable and fanned the malignancy of what ordinarily might have been a subacute membranous glomerulonephritis. There has been a great deal of work in which it has been argued that all patients with renal diseases are subject to pyelonephritis. If I had known she had pyelonephritis, I would have thought that the nephrotic syndrome and disease producing the nephrotic syndrome made her vulnerable to the pyelonephritis, but in this instance it seemed she may have had pyelonephritis for a long time with contracted kidneys and developed a superimposed nephrotic syndrome.

*Final Diagnosis:*

- (A) SUBACUTE MEMBRANOUS GLOMERULONEPHRITIS
- (B) CHRONIC PYELONEPHRITIS
- (C) NODULAR COLLOID GOITER
- (D) PERICARDITIS, MYOCARDITIS AND OSTEOPOROSIS SECONDARY TO RENAL INSUFFICIENCY

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# *Radiological Notes*

BERNARD S. WOLF, M.D.

CASE NO. 131

CASE SUBMITTED BY CLAUDE BLOCH, M.D.

This was a 65 year old female who was originally seen because of the complaint of a mass in the right parotid gland. The mass was not painful or tender and measured about 1.5 or 2 cm in diameter. No other pertinent physical findings were noted. A sialogram was performed on the right side and was said to have shown no abnormality. Aspiration biopsy of the mass was interpreted as suggestive of a mixed tumor. As a result, a superficial right parotid lobectomy was performed and originally reported as "chronic parotitis". The patient was then well for about fifteen months at which time she noted swelling of the left parotid gland. This appeared to be somewhat tender and compression of the left gland yielded thick viscid secretions via Stenson's duct. There was no evidence of a mass in the right parotid gland. A left parotid sialogram was performed and the picture obtained (Fig. 1) was quite remarkable. The main duct was well-delineated and normal in course and caliber. However, within the parotid gland itself, all of the canalicular duct radicles appeared to be narrowed into fine, short, linear channels. The gland was occupied by numerous spherical, smooth, small cystic areas measuring from 1 to 4 mm in diameter. There was no evidence of any discrete filling defect or mass within the gland. An evacuation study after acid stimulation revealed no significant emptying of the opaque material which had been introduced into the gland. The roentgen impression was that the patient was suffering from Mikulicz's disease. Review of the slides of the material removed from the right parotid gland was reinterpreted as consistent with Mikulicz's disease.

The characteristic sialographic findings in Mikulicz's disease is widespread cystic dilatation of the peripheral ducts, the so-called "mulberry pattern", in association with inability of the gland to empty itself normally. No abnormality is present in the main duct. This disease usually presents itself as a chronic symmetrical often painless swelling of the salivary and/or the lachrymal glands. On occasion, it may affect only a single gland acutely with marked pain and tenderness. The pathological changes have been described as consisting originally of periductal lymphocytic infiltration around the interlobar and interlobular central ducts. The inflammatory small cell response proceeds to fibrosis with loss of acini and with a decrease in number of the small ducts and widening of the remaining ductules. It is necessary to distinguish between Mikulicz's disease as described above and Mikulicz's syndrome. The latter represents symmetrical enlargement of the salivary and/or lachrymal glands as manifestations of systemic well-defined disease entities such as leukemia, lymphosarcoma, Hodgkin's disease or tuberculosis. In such instances, in the early stages, the gland is usually intact but adjacent lymph nodes are involved. At a later stage, the gland becomes secondarily involved. Originally, the sialogram in Mikulicz's syndrome reveals



no intrinsic abnormality but there may be displacement by extrinsic pressure on the ducts. Later, with invasion of the gland, there is a decrease in the arborization of the ducts and eventual obstruction to the main duct with consequent inflammatory changes, fibrosis and destruction of the gland.

*Case Report:* CHARACTERISTIC SIALOGRAPHIC CHANGES IN MICKULICZ'S DISEASE.



Case 131, Fig. 1. Left parotid sialogram shows no evidence of obstruction, filling defect or deformity of the main duct. Throughout the gland, there are numerous small cavities from 1 to 4 mm in diameter with intervening narrow, irregular ductules. There is no evidence of a mass within the gland substance.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Max Som.

#### CASE NO. 132

This was the first admission of a 35 year old male who about a month and a half prior to admission noticed that while walking his left hand pulled in and the thumb extended through the fingers. At the same time, the left calf muscle became tense and the left foot seemed to slump in walking and was somewhat weak. This entire episode lasted only twenty seconds and then completely disappeared. However, later in the day, he had another such episode. Since then, he experienced numerous similar episodes and these have increased in frequency and duration. Shortly before admission, on one day, the patient kept a tally of the episodes and counted 89 of them. Between attacks, he felt perfectly well ex-

cept for some fatigue. The movements during the episodes did not have the quality of convulsive movements. The attacks were always of a slow drawing internal rotation and acute flexion of the left wrist with the thumb through two fingers. The patient also complained of very slight numbness of the left side of the body from the top of the head to his toes and for a week before admission believed that the left side of his body was somewhat weaker than the right and that sensation in his left hand had diminished. Neurological examination demonstrated that pinprick and temperature sensibilities were decreased on the left half of the body below the neck. The left palpebral fissure was slightly larger than the right. There was questionable left facial asymmetry. Gait, power, and coordination were normal as were the deep reflexes. There was no Babinski sign. Vibration and position sense were normal. The pupils were equal and reacted to light normally. The ocular movements were normal and there was no nystagmus. Face and tongue movements were normal. Careful examination demonstrated some hyperesthesia of the right side of the soft palate with pulling of the uvula to the left on repeated phonation. No masses were palpable in the neck despite very careful examination. Compression of the left carotid artery produced some blurring of vision in the left eye. Compression of the right carotid artery produced no change. Blood pressure was 100/65. Pulse was regular. The heart was not enlarged and there were no other positive pertinent physical findings. Lumbar puncture showed the pressure to be within normal limits and the fluid to be clear. Sugar, protein, cell count, and Wasserman reaction of the spinal fluid were normal. After the lumbar puncture, the patient had several tonic motor seizures in the left hand and foot similar to those that he described prior to admission. Electroencephalogram showed no abnormality despite the fact that two of these seizures occurred during and after hyperventilation while the electroencephalogram was being performed. A pneumoencephalogram was performed without incident and without demonstrating any positive findings. Right carotid arteriography was then performed. The needle was inserted a short distance proximal to the bifurcation. The angle between the internal and external carotid arteries at the bifurcation was obviously increased with an arcuate curved bulging posteriorly of the internal carotid. In the angle between the two vessels, an ovoid area about 2 cm in length was opacified (Fig. 1A). There was no evidence of any broad communication of this region with the carotid vessels but there appeared to be several tortuous vessels supplying the opacified zone. Filling of the carotid vessels and their branches both intracerebrally and extracerebrally was normal. The structure which was opacified in the region of the bifurcation in the early arterial phases remained filled after the carotid vessels in the neck were emptied (Fig. 1B) but, in the last venous phases of the arteriogram, about seven seconds after the injection, the opaque area in the neck disappeared. The roentgen diagnosis of a carotid body tumor on the right side of the neck was made. It was, however, not clear whether this was the cause of the patient's symptoms since there was no apparent diminution in caliber of any portion of the internal carotid artery. In fact, the proximal portion of this artery appeared to be somewhat larger than would be normally expected. A left carotid arteriogram was subse-

quently done and demonstrated normal vessels in the neck as well as intracerebrally. On the left side, the angle at the bifurcation was very acute.

Despite skepticism that the patient's neurological symptoms and signs were attributable to the mass in the neck, this patient was explored. A mass about 2



Case 132, Fig. 1A. Percutaneous right carotid angiography. The needle is located in the common carotid artery a short distance proximal to the bifurcation. There is excellent filling of the external and internal carotid arteries and their branches. The bifurcation is widened by an ovoid opacified mass (arrow) which occupies the angle and displaces the internal carotid artery posteriorly. The opacification consists of a rather diffuse haze with numerous superimposed small tortuous vessels. There is no broad communication with the carotid vessels nor any premature venous visualization such as occurs in cases of arterial or arteriovenous aneurysms.

Case 132, Fig. 1B. Film taken about 3 seconds after Fig. 1A shows persistent opacification of the mass (between arrows). Opaque material disappeared from the neck 3 or 4 seconds later.

cm in diameter was found exactly at the bifurcation adherent to the proximal portions of both the external and internal carotid vessels. Moreover, the internal carotid artery, in addition to being displaced posteriorly by the tumor, was compressed and narrowed. By careful dissection, it was possible to free the tumor

from the vessels completely. The removed specimen, grossly and microscopically, had the characteristic features of a carotid body tumor without any evidence of malignant change. In the first week after the operation, the number of seizures markedly diminished and subsequent to this, the patient has had no seizures and has been completely well.

This patient is of considerable interest from both the clinical and the roentgen point of view. The number of cases of carotid body tumors visualized by carotid arteriography in the literature are few. Two cases diagnosed preoperatively have been described by Idbohln (1) and one case by Borrelli (2). The findings in these cases are identical to those illustrated by the current patient. The syndrome shown by this patient is quite rare in carotid body tumors which in the large majority of instances come to attention simply by the appearance of a mass. It is difficult to correlate the apparently good lumen of the internal carotid artery seen on angiography with the surgical findings. The fact that the artery was compressed in such a fashion that it was not visible on the roentgenogram in the lateral projection must, however, be accepted not only because this was evident at operation but because the patient's symptoms disappeared postoperatively and have remained gone now for a period of about six months.

*Case Report:* CAROTID BODY TUMOR WITH VASCULAR INSUFFICIENCY DEMONSTRATED BY ARTERIOGRAPHY.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Morris Bender and Dr. Max Som.

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#### CASE NO. 133

This was the first admission of a 29 year old female admitted with the chief complaint of paralysis of the right side of the body of two days duration. The previous history was completely noncontributory. One week prior to admission, she stated that she had had a mild upper respiratory infection. Three days before admission, while at work in the afternoon, she developed severe generalized headache and a feeling that something was in her right eye. The next morning when she awoke, she was dizzy with an unsteady gait. As related by the patient, this dizziness was a true vertigo. The next day, she noted weakness and clumsiness of her right hand. Her typing was poor and she was unable to put on lipstick. She began to drag her right leg and the right side of her face drooped. On the day of admission, the patient slipped, fell, hit her head and was unconscious for a minute or two.

General physical examination was noncontributory. Temperature on admis-



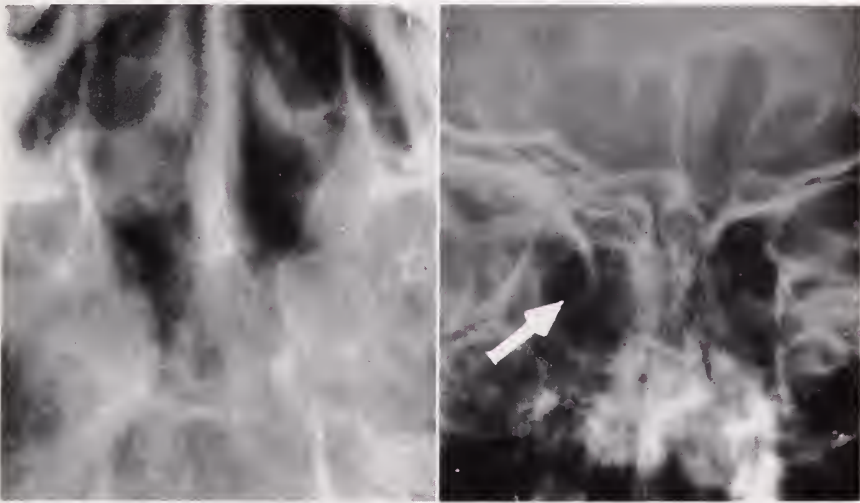
sion was below 100 but in the next four days ranged up to 101. Blood count showed a hemoglobin of 13 Gm per cent with a white blood cell count of 6,200 and 69 per cent polymorphonuclear leucocytes. Moderate toxic granulation of the leucocytes was described. Neurological examination showed no abnormality in the fundi. A right central facial paralysis was present. The tongue deviated toward the left. There was a moderately severe right hemiparesis with a Babinski sign on the right side. Eye movements were not remarkable and there was no evidence of nystagmus. No positive sensory findings were evident. A fairly severe ataxia and dysarthria were present with dragging of the right leg and inability to walk on the right foot. Lumbar puncture showed crystal clear colorless fluid with a pressure of 170 cm of fluid. The cell count showed 28 lymphocytes and 9 polymorphonuclear leucocytes per cu mm. The protein content was 53 mg per cent.

The progress of this patient was rapidly downhill marked by worsening speech, diplopia, the appearance of coarse nystagmus on upward and left lateral gaze, limitation of upward gaze and disappearance of the right corneal reflex. The picture took on the aspect of an advancing lesion of the midbrain and pons, inflammatory or demyelinating in character. Brain abscess was suspected. An attempt to perform a pneumoencephalogram was not successful. No air was seen in the ventricles after the introduction of 6 cc. This procedure did not have any deleterious effect on the patient. A left carotid angiogram was done. This demonstrated spreading of the cortical vessels and increased curvature of the anterior cerebral artery suggesting the presence of hydrocephalus or cerebral edema. The left posterior cerebral artery was well filled and there was also some filling of the right posterior cerebral artery from the left sided injection. In the frontal projection, asymmetry of the courses of the posterior cerebral arteries was noted but no definite conclusion could be drawn from the findings. The patient became stuporous and died rather suddenly. At autopsy, an elongated, large abscess was found in the left cerebral peduncle extending into the pons. In addition, an abscess was found in the sphenoid sinus. There was no evidence of a purulent meningitis but the arachnoidal tissues adjacent to the sella were congested and edematous. The possibility was suggested that an abscess of the sphenoid sinus was the original cause of this patient's disease and this was followed by an abscess of the brain stem, possibly as a result of a local thrombophlebitis. Culture of the pus showed enterococcus.

From a roentgen point of view, this case is of considerable interest because the simple films of the skull were not correctly interpreted. It was realized that in the lateral projection, the region of the sphenoid sinus appeared unusually dense (Fig. 1A). This was attributed to thickening of the base of the skull in the region of the middle fossa. Review of the film, however, indicates that within the dense body of the sphenoid there is a somewhat quadrilateral or irregular collection of air and that there is no clear-cut posterior bony boundary of the sphenoid sinus. A base view of the skull (Fig. 1B) shows none of the bony landmarks of the sphenoid sinus but, unfortunately, a base view of the skull is frequently not a satisfactory projection to visualize this sinus clearly. In the postero-anterior



Case 133, Fig. 1A. Lateral view of the skull. Except for a small area in its center (arrow), the body of the sphenoid sinus appears solid, *i.e.* unpneumatized. In contrast, the ethmoidal cells are well-developed and normally aerated. The "absence of the sphenoid sinus" should raise the suspicion that it is filled with inflammatory or neoplastic tissue.



Case 133, Fig. 1B. Base view of the skull shows no clear-cut bony walls of the sphenoid sinus. As in the lateral projection, the sphenoid sinus appears to be absent.

Case 133, Fig. 1C. In a slightly oblique PA projection, the superior and right lateral wall of the sphenoid sinus (arrow) can be identified by contrast with the air within it. The left lateral wall cannot be recognized in this or other projections. The abscess of the sphenoid sinus did not occupy the entire sinus.

projection (Fig. 1C), the roof and the right lateral wall of the sphenoid sinus were evident and the portion of the sinus visualized in this projection appeared to be well aerated. Nevertheless, this case demonstrates that, if on the lateral projection, the sphenoid sinus appears to be absent, this is likely to be the result

of serious and significant disease in the sinus, inflammatory or neoplastic. Inability to visualize the sphenoid sinus in the lateral projection in an older child or adult should not be attributed to failure of pneumatization. The fact that the sinus can appear relatively normal in the AP projection in such instances should not exclude this possibility since only a portion of the sinus is clearly seen in this view. When a suspicion exists of disease of the sphenoid sinus of this character, midline tomography in the lateral projection should be performed. It is striking in the present case that the ethmoidal sinuses are well-developed and show no roentgen features indicative of inflammatory change.

*Case Report:* ABSCESS OF THE SPHENOID SINUS AND ABSCESS OF THE BRAIN STEM. THE "ABSENT SPHENOID SINUS" SIGN.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Philip S. Bergman.

#### CASE NO. 134

This was the second admission of a 51 year old white male who had an "ulcer" history going back to the age of eighteen. Eleven years prior to admission, a gastroenterostomy had been performed for a duodenal ulcer. The patient did quite well until two years prior to admission when he started to complain of belching, eructations, and epigastric fullness. The symptoms increased in severity and his physician noted the appearance of an anemia. Despite symptomatic treatment, anemia persisted and epigastric pain increased in severity and frequency. A barium meal examination prior to admission was said to have shown a large gastric lesion on the posterior wall of the stomach. Despite strict medical regime for several weeks, the symptoms abated only slightly and a repetition of the barium meal examination showed persistence of the lesion. The patient was therefore, admitted for evaluation and operative intervention. Physical examination was essentially not contributory except for deep tenderness in the epigastrium and right upper quadrant. A well-healed upper abdominal scar was present. His anemia had been previously corrected by multiple transfusions. A barium meal examination was done on admission and after an interval of two weeks. At each examination, an ulcer crater was demonstrated on the posterior wall of the fundus of the stomach (Figs. 1 & 2). This crater was about 1.5 cm in maximum diameter and had the appearance of a niche with rather smooth shoulders projecting towards the lumen. The gastroenteric stoma was wide and barium left the stomach promptly through the stoma to enter both the afferent and efferent loops. There was no evidence of any marginal ulceration or abnormality in these loops. The stomach was not dilated nor did it contain any unusual amount of secretions. Some barium also left the stomach via the pylorus. The duodenal bulb was deformed.

Despite the fact that the roentgen features and the crater were essentially those of a benign lesion, it was felt on the basis of the clinical course of this patient and the rarity of a benign gastric ulcer in the presence of a well-functioning

gastroenteric stoma, that the most likely diagnosis was carcinoma of the fundus of the stomach. At operation, this appeared to be confirmed by the presence of adhesions and a mass in the region of the fundus of the stomach extending to the



Case 134, Fig. 1. Barium meal examination shows a large niche (upper arrow) on the posterior wall of the stomach near the cardia. The ulceration is sharply outlined with smooth shoulders projecting towards the lumen on each side. The anastomosis (lower arrow) is located low on the greater curvature aspect of the body of the stomach. Barium left the stomach promptly through the wide stoma.

cardia, with numerous enlarged lymph nodes. Examination of the stoma and the afferent and efferent loops of jejunum showed that these areas were not remarkable. Multiple biopsies of the lymph nodes were reported on frozen section as inflammatory. The fundus and the esophagogastric region were therefore mobilized and in the most proximal portion of the stomach a perforated ulcerative lesion was found about 2 cm in diameter. Somewhat proximal to this area there was another indurated lesion about 1 cm in diameter near the esophagogastric junc-



tion. An esophagogastrrectomy was performed leaving the distal portion of the stomach with the attached gastroenterostomy untouched. Histological examination of the ulcerated lesions in the stomach showed them to be typical chronic peptic ulcers with no evidence of carcinoma. Postoperatively, the patient's course was unusually satisfactory and he was discharged three weeks after operation fully ambulatory.



Case 134, Fig. 2. Findings two weeks later are identical to Fig. 1. The ulcer crater filled with air (between upper arrows) is unchanged. The unusually great width of the stoma (between lower arrows) is well-demonstrated.

The occurrence of a benign peptic ulcer of the stomach in the presence of a well-functioning gastroenterostomy without marginal ulceration is distinctly uncommon. It is also of interest that in this patient the gastric ulceration was resistant to treatment. While the possibility in such cases of the Zollinger-Ellison syndrome must be considered, there is no evidence in the current case to suspect that a pancreatic or other endocrine adenoma is present.

*Case Report:* CHRONIC BENIGN PEPTIC ULCER OF THE STOMACH RESISTANT TO TREATMENT IN THE PRESENCE OF A WELL-FUNCTIONING GASTROENTEROSTOMY.

## ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Bernard Friedman and Dr. Raymond S. Megibow.

## CASE NO. 135

This was the eleventh admission of a 14 year old white male known to be suffering from  $\text{AHG}$  deficiency hemophilia. On the morning of admission, the patient noted some rumbling on the left side of his abdomen and, shortly after, passed about "8 pints" of bright red blood per rectum. Seven hours later, he passed some stool as well as half a pint of darker blood. A week prior to admission, the patient



Case 135, Fig. 1A. Barium enema shows a segment in the distal descending colon of limited distensibility. No normal haustral pattern is evident in this area. The folds appear to be thick or closely spaced probably because of limited extensibility of the bowel wall in a longitudinal direction. The medial wall (arrow) is flattened as by an extrinsic or intramural mass.

complained of some constipation and difficulty in moving his bowels associated with some mild crampy left upper quadrant pain. Three years prior to admission, he had experienced an episode of crampy abdominal pain and constipation and noted small amounts of blood mixed with stool. At that time, he was said to be suffering from "spastic colon" and responded well to stool softeners. Previous



Case 135, Fig. 1B. Evacuation film shows an eccentrically narrowed segment (arrow) in the distal descending colon with coarse, amorphous appearance of the fold pattern.

admissions to the hospital were the result of hemarthroses involving the left knee and the left elbow as well as nose bleeds. There had been one episode of hematuria. On each occasion, the patient responded well to infusions of fresh frozen plasma. Three years prior to admission, the patient was said to have suffered from infectious hepatitis at the same time as his sister. Both siblings apparently recovered without any complication. Examination on admission showed a pale, thin adolescent in no acute distress who appeared younger than his stated age. An ecchymosis was present over the right elbow with some limitation of exten-

sion of this joint. Joint mobility at the left knee and left elbow was diminished. The abdomen was soft, flat, and nontender. The examiner believed he could feel masses of stool in the left upper quadrant. Temperature was normal; blood pressure was 100/40; and pulse was 96. Hemoglobin by the Sahli method was 7.5 Gm.

The patient was promptly treated with intravenous fresh frozen plasma. Despite this, however, considerable quantities of blood were passed per rectum over the next four days. The blood in the stool at times consisted of blood clots and at other times was of a currant jelly character, but some liquid blood was also seen. Five days after cessation of bleeding, a barium enema was performed (Figs. 1A & 1B). There was no obstruction to the retrograde flow of barium or evidence of an intraluminal filling defect. However, an area in the distal descending colon  $2\frac{1}{2}$  inches in length showed limited distensibility, particularly on its medial aspect and the haustral pattern in this area was abnormal. The fold pattern was somewhat thickened but there was no evidence of ulceration or extravasation. In view of the clinical picture, these findings were interpreted as the result of an intramural, presumably submucosal, hematoma.

In a limited experience, bleeding from the gastrointestinal tract in a hemophiliac has been most commonly due to a colonic lesion. This apparently is not of a diffuse character or mucosal in origin, but is the result of a fairly discrete intramural hemorrhage with hematoma formation. It must be assumed, however, that a tear in the mucosa is associated with intramural bleeding from a sizable vessel. The history of episodes of constipation in this patient is of interest since it may be related to unusual strain on the bowel wall or trauma due to inspissated stool.

*Case Report:* INTRAMURAL HEMATOMA OF THE COLON IN HEMOPHILIA.

## JUVENILE POLYPS ("ADENOMAS") OF THE COLON— CLINICAL AND ROENTGEN FEATURES\*

BERNARD S. WOLF, M.D., MYRON MELAMED, M.D., AND  
ROBERT TURRELL, M.D.

Polyps of the rectum and colon in children are not rare. Helwig in an autopsy study of 449 individuals under the age of 21 demonstrated an incidence of polyps of the rectum or colon of about three per cent (1). While the term polyp may be used in a general sense to refer to any intraluminal projecting mass, it is more commonly used, as in this report, to refer to benign epithelial growth. In children, polyps are of two different, quite distinct, types. One type is clearly adenomatous and similar in all respects to the adenomata found in congenital polyposis and in adults. The second and much more common variety is the "juvenile" polyp (2) which, while containing adenomatous structures, shows prominent large cyst-like glands (Fig. 1), abundant connective tissue stroma

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and significant, often marked, inflammatory cell infiltration sometimes with a preponderance of eosinophiles. The adult type of adenomatous polyp is quite rare in children and occurs usually as part of congenital polyposis (3). Polyposis



Fig. 1. Low power photomicrograph of a juvenile polyp shows numerous large cyst-like glands and abundant connective tissue stroma. In many areas, numerous inflammatory cells could be seen with higher magnification. The surface epithelium is flat with relatively few glandular pits. Ulceration of the surface epithelium is frequently present.

of this type has an extremely high incidence of carcinomatous change. In marked contrast, however, the juvenile variety rarely if ever becomes malignant and, in fact, there is doubt that such growths should be considered as true tumors at all. The possibility that the juvenile type of polyp is of inflammatory origin, perhaps superimposed on a developmental defect, has been suggested. It has also been indicated that juvenile polyps disappear spontaneously and that, if the correct diagnosis is known, surgical extirpation is not required (2). From the point of

view of etiology, it is of considerable interest that juvenile polyps are unusual before the age of one year, that the incidence is maximum at about the third or fourth years, and is again quite low after the age of 11 or 12. It must be extremely rare for the juvenile type of polyp to be found in the adult. The fact that occasionally siblings or parents also give a history of colonic polyps does not necessarily indicate that the disease process is due to congenital polyposis, since juvenile polyps may also be familial. Moreover, in a significant number of cases, juvenile polyps are multiple. Of eighty patients seen by the authors, 66 showed solitary polyps, 18 had 2 or 3 polyps and one patient had 6 small polyps. There appears to be no remarkable difference in sex incidence. Incidentally, the villous or papillomatous type of polyp seen in adults especially in the older age groups has apparently not been reported in children.

The presenting symptoms in children with juvenile polyps are bleeding from the rectum, blood streaked mucus or stool or protrusion of a polyp ("a cherry") through the anus (4). If the polyp is located more proximally in the colon, recurrent abdominal pain may occur, presumably as a result of periodic intussusception. Occasionally, there may be episodes of diarrhea and the combination of pain, diarrhea, and bloody stools may mislead the clinician to the diagnosis of ulcerative colitis. Bleeding may be sufficiently severe and recurrent to cause marked anemia. In one patient admitted to this hospital, the hemoglobin was 6.6 Gm per 100 cc.

From the roentgen point of view, the juvenile polyps above the reach of the sigmoidoscope are of greatest interest. According to Kerr, about thirty per cent of polyps in children occur proximal to the rectosigmoid (3). In our experience, approximately ten per cent have been located in the colon and not visible on sigmoidoscopy. These have all been located on the left side of the colon, that is, between the splenic flexure and the rectosigmoid. It is rather surprising that no case of a juvenile polyp on the right side of the colon was seen in this group of 80 children. Polyps beyond the reach of the sigmoidoscope, of course, must be discovered by barium enema examination. In many instances, however, in which the polyp is located in the rectosigmoid or rectum, the pediatrician has requested barium enema examination in preference to sigmoidoscopy as the first investigative procedure. This has been done presumably because, in the opinion of the pediatrician, a barium enema examination is less exacting. Nevertheless, barium enema examination in children is notoriously difficult, not only because of poor cooperation on the part of the patient, but also of considerable difficulty in securing the cooperation of the physician to adequately prepare the bowel. As a result, even a large polyp may be completely obscured by stool. Multiple examinations with special attention to the evacuation films and double contrast visualization are frequently necessary (5). In any child in whom a polyp has been discovered on sigmoidoscopy, barium enema examination must be performed in order to determine whether additional lesions are present. By the same token, if a polyp has been discovered on barium enema examination, sigmoidoscopy should be performed in order to determine whether additional lesions are present in the rectum.

The roentgen features in the children in whom a juvenile polyp has been discovered on barium enema examination have been rather consistent. This is probably due to the fact that only the larger lesions come to barium enema examination since small lesions in the colon are likely to be asymptomatic. At any rate, the colonic lesions that have been found have been, proportionately, considerably larger than the usual adenomatous polyp found in the adult. The average size has been between 2 and 2.5 cm (Figs. 2-4). An obvious pedicle has been present in

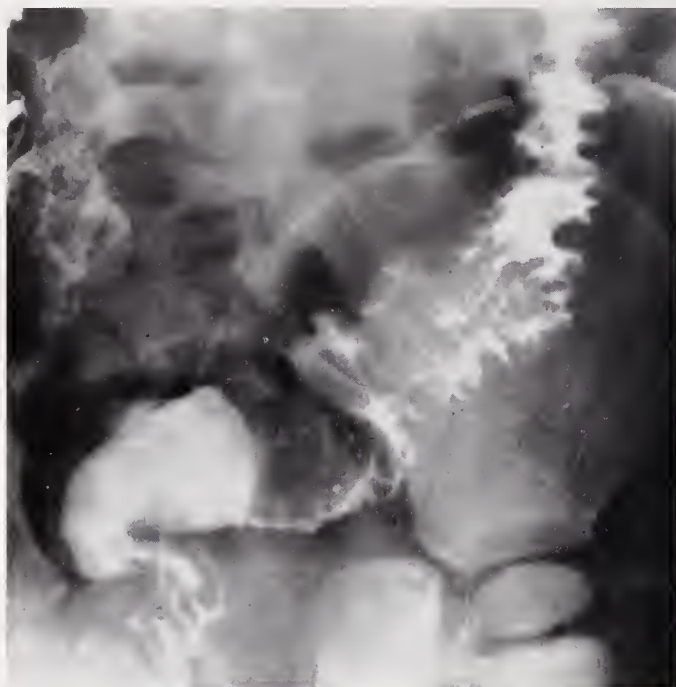


Fig. 2. Juvenile polyp in a 14 month old child. A long thin pedicle is attached to the distal descending colon. The body of the polyp in the sigmoid is round, sharply outlined, fills and distends the lumen.

each instance and in some cases, the pedicle has been extraordinarily long (Fig. 2). In contrast to a somewhat mulberry appearance of an adult adenomatous polyp, the surface of a juvenile polyp is smooth and sharply demarcated (Figs. 2-4) with little evidence of lobulation. This rather punched-out appearance may in some instances be quite striking. We have not seen any evidence of significant or deep ulceration on the surface of such a juvenile polyp, nor have we observed the entrance of any barium into the cyst-like spaces present within these lesions. The size and shape of the polypoid mass changes little, if at all, with various degrees of filling of the colon or after evacuation. This indicates that the tumor as would be expected from the presence of inflammatory changes within it is relatively firm in consistency. At the point of attachment of the polypoid mass, there



Fig 3A. Juvenile polyp in a 3 year old child. The filled colon shows a very sharply outlined, smooth, ovoid defect in the mid-descending colon (lower arrow) with a rather broad pedicle (upper arrow) attached proximally.



Fig. 3B. Air contrast study confirms the sharp, smooth outline of the polyp (lower arrow) and the rather long thick pedicle (upper arrow). The size and configuration of the defect is constant.



is no evidence of rigidity of the wall of the colon and no irregularity in the contour except for a short defect or dimple at the site of attachment of the pedicle. As pointed out above, it is important not to overlook the fact that such lesions may be multiple.

From a therapeutic point of view, treatment of juvenile polyps is relatively simple if available to sigmoidoscopic therapy. Surgical diathermy without anesthesia can be safely employed for the eradication of small to moderate-sized lesions occurring on the posterior and lateral walls of the rectum below the peritoneal reflection in cooperative children. In all young children and infants, however, as well as in noncooperative older children, all polyps situated above

Fig. 4. Juvenile polyp in a 2½ year old child. A large, sharply demarcated, smooth globular defect is present in the descending colon. Despite the fact that the defect occupies the entire diameter of the lumen of the colon, there is no evidence of obstruction. A contour defect is present on the lateral wall of the colon at the level of the lesion. This represents the site of attachment of the polyp to the wall. Most of the pedicle, however, is obscured by the overlying bulk of the defect.



the peritoneal reflection but within the reach of the sigmoidoscope should be treated in the hospital under anesthesia to avoid inadvertent motion by the patient during electrocoagulation. Pedunculated polyps are removed at the mucosal base by means of a high frequency snare. In those lesions situated above the reach of the sigmoidoscope, transabdominal colotomy with severance of the stalk close to the base should be employed. A segmental resection for juvenile polyps should rarely if ever be required.

#### ACKNOWLEDGMENT

The authors wish to acknowledge the cooperation of Dr. Ernest E. Arnheim in the preparation of the case material.

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# Abstracts

## *Papers Presented before the Research Club of The Mount Sinai Hospital*

*New York, N. Y.*

*Angiotensin II in Normotensive and Hypertensive Human Subjects.* Robert L. Wolf, M.D., Milton Mendlowitz, M.D., Julia Pick, B.S., Stanley E. Gitlow, M.D., and Nosrat Nafteli, M.S. (Department of Medicine.) Presented November 14, 1960.

Angiotensin II- $I^{131}$  has been intravenously administered to normotensive and hypertensive human subjects. The plasma radioactivity after injection has been studied by electrophoretic and chemical analysis. Approximately one-third of the total blood radioactivity is in the erythrocytes and the remaining two-thirds is in the plasma. The rate of disappearance of plasma radioactivity after angiotensin II- $I^{131}$  administration is more rapid in the five normotensive control patients than in three subjects with essential hypertension.

The five normotensive subjects have smaller apparent spaces of distribution and more rapid degradation rates of angiotensin II than the three subjects with essential hypertension. The mean values for the apparent volumes of distribution of angiotensin II are approximately 23 liters in the normotensive subject and 29 liters in subjects with benign and malignant hypertension.

The total amounts of angiotensin II which are present in the body and which are readily exchangeable with the blood angiotensin II may be calculated to approximately average 0.41  $\mu\text{g}$  in the normotensive subject, 1.10  $\mu\text{g}$  in the two subjects with benign essential hypertension and 9.3  $\mu\text{g}$  in the malignant hypertensive subject.

*Serum Proteins in Normal Human Gastric Juice.* Nathaniel Cohen, M.D., Martin I. Horowitz, Ph.D. and Franklin Hollander, Ph.D. (From the Gastrointestinal Physiology Research Laboratory, and the Division of Gastroenterology, Department of Medicine.) Presented November 14, 1960. (Supported by Grant C-288, U. S. Public Health Service).

Previous reports from this laboratory have shown that serum albumin and serum globulins are present in antacid gastric secretions from dogs' Heidenhain pouches. Gullberg and Olhagen have recently found serum albumin in normal human gastric juice when phosphate buffer was first instilled into the stomach to prevent acid proteolysis, but they did not quantitate the amount of albumin or evaluate the possible contribution of saliva. In addition, no quantitative data have been available concerning gamma globulin in normal human gastric juice. The present study was undertaken to quantitate the albumin and gamma globulin content of human gastric juice and to evaluate swallowed saliva as the possible major source of these proteins.

$I^{131}$ -labeled human serum albumin was administered intravenously, and neutralized gastric juice was collected by orogastric aspiration following intragastric instillation of phosphate buffer (pH 7.2-7.4). Contamination by saliva was mini-

mized by continuous suction from the mouth. Albumin constituted 2.3–36.7 per cent of the protein content of such gastric aspirates from nine human subjects without gastrointestinal disease. The concentration of radioactive albumin in simultaneously collected saliva was sufficiently low to exclude swallowed saliva as the only source of the albumin found in the gastric aspirate. Similar studies in five human subjects utilizing  $I^{131}$ -labeled human serum gamma globulin demonstrated this protein to constitute 0.8–7.0 per cent of the total gastric juice protein; saliva again was found to contain an insufficient amount to be the only source of gamma globulin in the gastric contents.

*The Influence of Various Solutions Bathing the Gastric Mucosa on the Hydrogen Ion Concentration of the Secreted Fluid.* Mario Altamirano, M.D., J. Lawrence Werther, M.D. and Franklin Hollander, Ph.D. (From the Gastrointestinal Physiology Research Laboratory.) Presented January 12, 1961. (Grants A-3945 and A-2290, N.I.H., U.S.P.H.S.; L.W.—Trainee in Gastroenterology, U.S.P.H.S. Training Program Grant 2A-5126.)

A segment of the greater curvature of dog's stomach, with intact circulation, was mounted in a chamber with the mucosa upwards, as described elsewhere by one of us (M.A.). Into this chamber 25 ml of a test solution was introduced for a predetermined time interval, at the end of which it was aspirated completely by gentle suction, and the concentrations of  $H^+$  and  $Cl^-$  were determined. Test solutions were distilled water and NaCl, glucose, or glycine in various concentrations. Each experiment (31 in all) comprised 3 phases: (I) *Resting phase* (3 half-hour periods); no stimulus. (II) *Conditioned phase* (2–3 hours, divided into periods of 30 minutes or less); stimulus intramuscular histamine every half hour. (III) *Free secretion phase* (2 or 3 half-hour periods without test solution); same stimulus. From volume and concentration data of I and II, an estimate was made of the  $H^+$  concentration of the primary acid secretion, conditioned by the particular test solution. In all cases, this acidity was higher than that for free secretion in the same experiment (135–164 mEq/L, average 152). Gastric mucosa bathed by these solutions puts out less water per mEq of  $H^+$  than without them. Water output per unit time was proportional to  $\log H^+$  concentration of gastric contents.



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THE JOURNAL OF  
THE MOUNT SINAI HOSPITAL

## DISTURBANCES OF RESPIRATION OF FUNCTIONAL ORIGIN

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There is no organ in the body that may not be affected by psychic disturbances. Emotional influences cause disturbances primarily in the function of the organs and this led to the designation of these conditions as *functional diseases*. Admittedly, this term is not a good one since functional disorders also result from anatomical alterations in organic disease. Moreover, the alterations in function which result from psychic abnormalities eventually can cause organic disease. The recognition of this aspect of the problem has given rise to the term *psychosomatic diseases* for those in which psychic influences are the initial cause of the illness. On the other hand, primary organic diseases can lead to psychic alterations which may produce additional symptoms that color the entire picture.

Obviously the dividing point between pure functional derangement due to mental influences and organic disease secondary to this, as well as the effects of the mental reaction of the patient to an organic disease, cannot be sharply drawn. There is, however, a group of clinical manifestations which are purely psychic or nervous in origin. In many individuals these cause particularly striking effects on the respiratory tract. In addition to delineating the external clinical manifestations of the functional derangement, some of the psychological mechanisms involved in the production of these symptoms will be analyzed insofar as possible. Where secondary organic changes take place, their pathogenesis will be discussed. Finally, methods used to control the functional disturbances will be indicated.

## SIGHING RESPIRATIONS

Perhaps the most common form of respiratory disturbance of psychic origin brought to the attention of the clinician is that characterized by irregularity of respiration. The patient complains that he has difficulty in breathing, and usually this is all that he is able to say concerning the nature of his difficulty unless aided by proper questioning. The patient will then state that he does not feel as if he gets enough air and must therefore take deep breaths. Breathing is otherwise unimpeded. The symptom alone may be distressing enough to influence the patient to consult a physician. He fears that he may have a serious disease of his heart or lungs. In addition, there are often associated symptoms, either psychically or organically determined, which make him seek medical help. The altered respiration is then either one among several psychogenic symptoms or the result of psychogenic overlay in a patient who has organic disease.

The patient may not be able to explain the exact nature of his respiratory

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difficulty despite questioning. He may simply state that he feels a sense of heaviness in his chest as if he is not getting enough air. The characteristic sudden deep inspiration, often accompanied by an exaggerated, noisy inspiration, is noticeable during the taking of the history or the performance of the physical examination. Since it is most frequently a manifestation of anxiety, the symptom is usually present at the visit to the doctor's office when the patient's anxiety is accentuated. When his attention is called to this type of respiration, he will state paradoxically that his inability to get in enough air causes him to take a deep breath. The expiration following the forced inspiration is usually prolonged and has a sighing character which has given rise to the term sighing respirations.

We have no reason to believe that the deep inspiration is required because of oxygen want, nor is there any evidence that a prolonged expiration is required for the elimination of excess carbon dioxide as a result of inefficient breathing immediately before the sighing respiration occurs. On careful observation one will note that there is a pause in breathing after the forced respiration to make up for the long inspiration and expiration that were not required to satisfy a functional need.

Breathing is normally an unconscious act. Physiological mechanisms control its depth and frequency, and establish a well regulated periodicity. However, when attention is focused upon the breathing process and brings it to the conscious level, the periodicity is interfered with and abnormalities such as this occur. In the treatment of sighing respirations, therefore, the patient requires complete reassurance that he is not suffering from organic disease of his heart or lungs to relieve anxiety that keeps his breathing in the conscious sphere. While it is true that assurance may be achieved by carefully chosen words and by the personality of the physician, this is usually insufficient. The patient must also be given the benefit of a thorough examination so that he may be completely convinced that no disease is being overlooked. The thoroughness of the examination should be emphasized before the patient is told that he is not suffering from organic disease. If the mechanism of the production of his symptom is then explained to him, he will be in a position to disregard it and relegate his respiration to the unconscious sphere where it belongs.

#### DYSPNEA

True dyspnea without organic disease may be caused by a functional disturbance at different levels in the respiratory tract. The difficulty may lie in the movement of the chest wall or diaphragm. Respiration may be impeded by bronchial spasm or even bronchorrhea without organic influences, or by psychogenic spasm of the muscles of the throat or larynx which shuts off respiration.

#### *The Chest Wall*

Muscular weakness occurs commonly in those who are affected with a psychoneurosis. Since this is frequently the predominant symptom in nervous people, the term "neurasthenia" was in vogue for many years. The muscular

weakness in neurasthenia often causes the patient to complain that all movements are accomplished only with great effort. This complaint may also be referred to the respiratory muscles of the chest wall. Breathing then is fraught with effort and thus causes dyspnea.

It is quite possible that the muscular difficulty in neurasthenic individuals is partly due to poor coordination between the extensor and the flexor muscles. This may very well apply to the muscles of the chest used in breathing. If the set of muscles which should be relaxed, undergo contraction during inspiration, the work of the normally contracting muscles becomes more difficult. This would increase the work of breathing and add to the tendency to dyspnea.

Discoordination of the respiratory muscles may reach an extreme form and actually result in dissociated movement of the different sets of respiratory muscles. Respiratory dissociation is most frequently noted among those who make a habit of thoracic breathing. The motion of the diaphragms may be limited or there may even occur, during attacks of hysteria, complete relaxation of the diaphragm during inspiration. Under the latter circumstance, particularly when the patient is in the recumbent position, the diaphragmatic leaves rise in response to the negative pressure in the thorax during inspiration. Vigorous contraction of the intrinsic and accessory muscles of the chest wall, resulting in pronounced expansion of the chest, is then required for normal ventilation. The great increase in the work of breathing thus entailed may cause severe dyspnea.

The paradoxical breathing may reach an extreme form in rare instances of hysteria, when, as described by Oppenheim, the muscles on one side of the chest relax during inspiration while the movements on the other side are normal. This form of paradoxical breathing is analogous to that which occurs immediately after extensive thoracoplasties. Breathing then is accomplished by only one side, and that side obtains some of the air expelled from the opposite lung which is in a state of exhalation. The air inspired on the normal side is mixed with air low in oxygen and high in carbon dioxide, resulting in severe dyspnea and even cyanosis.

### *The Diaphragm*

Everyone who has had occasion to perform many fluoroscopic examinations of the chest has noted that some patients move the diaphragm little or not at all during the procedure. Moreover, it appears to be impossible to teach some of them to move the diaphragm during the fluoroscopy. The same is often true during examination of the abdomen. When asked to breathe in deeply, the patient fails to use the diaphragm, making palpation of the abdominal viscera difficult. However, one may note normal abdominal movements when the abdomen is not being examined or when the patient is not being fluoroscoped. Merely calling the attention of the patient to the act of respiration, *i.e.* bringing respiration into consciousness, frequently results in pure thoracic breathing.

In neurotic individuals who complain of dyspnea, failure to use the diaphragm is often the cause of the symptoms. When examining the abdomen or fluoroscoping the patient, I frequently find it useful to tell the patient not to make any at-



tempt to breathe in deeply but simply to suck in air. This de-emphasis of the breathing motion usually suffices to induce the patient to use his diaphragm in a normal manner. Consciousness of breathing is thus one of the causes of dyspnea. On the other hand, dyspnea makes one conscious of respiration, thus forming a vicious cycle.

Lag in the motion of one leaf of the diaphragm, usually the right, may occur under conditions of mental stress. Thus, during fluoroscopy of the apprehensive patient, one may note, when the patient is told to take a deep breath, that the right leaf of the diaphragm stands still at the beginning of inspiration and then slowly descends after the left leaf has descended completely. In fact, a slight elevation of the affected diaphragmatic leaf may precede its descent. This form of paradoxical respiration is functional and does not indicate weakness of the diaphragm or improper innervation through the phrenic nerve. In such instances one may induce a return to normal respiration by engaging the patient in conversation to distract his attention from the breathing process. Diaphragmatic motion may also be observed to be normal if the patient is told to make a prolonged forced expiration without asking him to inspire voluntarily. This functional disturbance, which is not infrequent among relatively stable people, is more common among those suffering from psychoneurosis, and is even more frequent among those with severe hysteria.

A most alarming clinical picture may be produced by bilateral diaphragmatic spasm or flutter, rare occurrences which may be associated with organic disease. However, they have been described, and we have seen them, as purely hysterical manifestations. When both leaves of the diaphragm remain constantly contracted the lungs are overinflated, and inspiration requires the use of the accessory respiratory muscles if the patient is to move sufficient air. The overstretched lungs call forth a Hering-Breuer reflex during inspiration, inhibiting the intake of the air required. The patient is then cyanotic and in acute distress. There is tachypnea to make up the deficiency of inspiration by an increase in the respiratory rate. The picture simulates an acute asthmatic attack. However, there is no wheezing or other evidence of bronchial spasm, while the roentgen appearance is the same as that of the acute emphysema that occurs in asthma.

### *The Bronchi*

Normally the bronchi are relaxed during inspiration and contract in expiration. The expiratory contraction of the bronchi is accentuated when there is spasm of the bronchial musculature although they are also narrowed to some degree during inspiration. While inspiratory wheezing rales are present during an acute attack of asthma, the expiratory rales are more prominent, and expiration is prolonged because of the increased contraction of the bronchial musculature during the expiratory phase. Whereas the abnormal contraction of the bronchi, in most instances, is due to bronchial irritation as in acute bronchitis, or as a manifestation of an allergic reaction, it may also be the result of purely psychic influences.

Most often psychogenic asthma occurs in a person who has already had

bronchial spasm either from a bronchial infection or from an attack of allergic asthma. In children particularly, even when there has been no allergic manifestation in the patient or his family, chronic or recurrent asthma has been observed to follow an acute respiratory infection. Acute bronchitis results in spasm and dyspnea with noisy respirations. The child notes the anxiety of those about him and relishes the attention bestowed upon him. He quickly learns to reproduce the bronchial spasm with its accompanying terrifying effects. This may remain with him as a subconscious mechanism. He may use it as a method of protection or rebellion or as a means of focusing attention on himself when either a conscious or an unconscious need arises within his psyche.

Because of the danger of the establishment of a confirmed asthmatic state, the parents should be instructed to appear to disregard the wheezing when their child develops an acute bronchitis. In adults as well, the physician should be on his guard not to call the attention of the patient to the wheezing rales that he hears during the examination. He should particularly refrain from mentioning the word, "asthma," in such cases. My observations over a period of many years leave me with the impression that calling attention to the wheezing and the use of the word asthma in the hearing of a neurotic patient with an acute bronchitis may perpetuate the bronchial spasm.

It has been said by some that all asthma is psychogenic. I do not believe that this is true. However, I am convinced that the great majority of patients who have asthma are also suffering from a psychoneurosis. In a great many there are distinct evidences of a neurotic pattern of behavior before the onset of the asthma. In others, the difficulties imposed by the asthma are sufficient to bring about a neurotic pattern. In many it is justified to conclude that the tendency to bronchial spasm is enhanced by psychic factors. This is one of the reasons why it is so difficult to cure bronchial asthma even if the allergic and infectious components are controlled.

Hypersecretion of the mucous membranes in various parts of the body may be the result of emotional disturbances. In rare instances, bronchial hypersecretion without bronchial spasm may be due to this cause. The sputum is profuse in amount, perfectly clear and mucoid. Wheezing, as well as bubbling rales, may be audible but disappear after coughing. In this way, obstruction of the bronchi by secretion may be differentiated from bronchial spasm.

Not infrequently the lungs and bronchi of a patient who has a tendency to bronchial spasm may seem to be perfectly clear, but the spasm may be brought into evidence by having the patient cough repeatedly or make a forced expiration. Bronchial rales are accentuated by these maneuvers if they are due to spasm, but are diminished markedly or disappear if they are due to obstruction of the bronchi by secretion. Thus, examination before and after induced coughing and during forced expiration is an important method for differentiating between bronchial spasm and secretion.

The sputum examination may be very helpful in the diagnosis of psychogenic bronchorrhea. On microscopic examination little is to be seen aside from the mucus. There are few leukocytes and no eosinophiles or fibrin strands. The nose

should also be carefully examined to make certain that there is no evidence of a vasomotor rhinitis which might be of allergic origin. Certainly an x-ray examination of the chest should be performed to exclude any possibility of adenomatosis which causes a similar type of secretion. Relief may be obtained regularly by the use of atropine in addition to a mild sedative.

### *The Larynx*

Spasm of the larynx or supralaryngeal muscles may effectively shut off respiration temporarily. The patient feels as if he is choking to death and may actually lose consciousness. However, the spasm is relieved soon after this occurs and normal respiration is then resumed. In the meanwhile the patient undergoes all of the mental as well as the physical effects of strangulation. This is indeed a terrifying experience. The physician who arrives to see the patient, invariably after the attack is over, usually will think first of a sudden edema of the larynx or of the base of the tongue, but examination shows these structures to be normal.

This type of spasm is undoubtedly psychically induced. It differs from the breath holding of children, accomplished for the sake of impressing the parents, because the attacks may occur even if no one is present. It may represent an unconscious attempt to fulfill a death wish.

A clue to the therapy occurred to me when I first encountered this condition, many years ago, in a young girl who had had several such attacks during the night when alone. She also had them during the daytime so that she was afraid to leave the house. During the course of questioning it developed that her father, to whom she was closely attached, died in her arms during a heart attack, and the gurgling death-rattle which she heard at that time never left her mind. It was soon after this that her attacks began. It occurred to me that the spasm might subside if she consciously held her breath, making no attempt at inspiration for a period of fifteen seconds. She was instructed always to have a watch with a sweep second-hand near her person. It was proved to her that she would undergo no harm if she held her breath for fifteen seconds. It was then suggested to her that the spasm would be automatically relieved by that time. After this she found that the spasm and the sense of choking subsided within a few seconds of breath holding. The attacks stopped soon after she began this method of control.

Similar spasms occur occasionally in hysterical individuals during a paroxysm of coughing. The patient is unable to inspire adequately before the reflex cough is repeated, causing a sensation of choking. In rare cases the paroxysmal cough may be associated with a complete closure of the glottis by the muscular spasm which becomes intensified by efforts to breathe in, cutting off inspiration completely. Since no air can enter the lungs, the patient is unable to cough. Here also the spasm may persist until the patient becomes unconscious. This is undoubtedly the mechanism of "post-tussive syncope."

In most of the attacks the spasm is relieved before unconsciousness takes place. Minor attacks may be exhibited by the patient while being interviewed. He has a spell of coughing, each cough being less vigorous as less and less air is expelled.

and finally he goes through forceful motions of inspiration through a practically closed off larynx. He becomes intensely cyanotic but after a number of seconds is finally able to take a complete inspiration at which point the attack is terminated.

The patient may enter the office with evidence of injuries sustained during an attack. While the shutting off of the glottis is a manifestation of hysteria, the loss of consciousness in post-tussive syncope is organically determined. The syncope is due to cerebral anoxia resulting from interference with return flow of circulation from the brain. This, in turn, is caused by increased intrathoracic pressure resulting from the failure to make an inspiration between the successive coughs. Thus, post-tussive syncope differs from the fainting spells associated with other forms of hysteria in which the patient is not likely to injure himself.

Here again the effective treatment is voluntary breath holding. It is demonstrated to the patient that he can hold his breath voluntarily for anywhere from twenty seconds to a full minute without harm. I have found that holding the breath for as little as five to ten seconds is sufficient to relax the spasm and restore normal breathing.

#### COUGH

Psychogenic cough may occur in two forms. It may be more or less constant or it may occur in paroxysms. In the former instance, the patient will usually admit that the cough is more frequent when he is emotionally upset. Generally the cough is short and not preceded by an inspiration. In some instances it is exceedingly loud and barking, particularly when the patient is in the company of others. The cough is often most noticeable while the patient is sitting in the waiting room, and it may stop when he is busily explaining his symptoms. It is always dry, and generally can be controlled sharply at the command of the physician.

The paroxysmal cough occurs particularly at night. Severe attacks are associated with choking sensations. One cough may follow another so quickly that the patient fears he will not be able to catch his breath at all and will choke to death. He states that the cough is essentially dry. Nevertheless, he feels that something is blocking his throat and finds that the paroxysm ends when he finally brings up a small amount of sputum. Observation of the cough and of the tiny fleck of clear secretion brought up at the end of the paroxysm makes one wonder why the expectoration of such a small amount of innocuous sputum should relieve the attack.

The paroxysmal attacks almost always begin in the wake of an acute respiratory infection. The patient usually states that the symptoms began with a cold and that during the first few days he brought up a considerable amount of sputum with ease. This appeared yellowish, indicating its infectious origin. Later the cough became dry and he was able to bring up sputum only with a prolonged spell of coughing.

The only conclusion that I have been able to reach is that the conditioned reflex of coughing to bring up sputum has been ingrained in the patient, that the



dry cough is psychically induced and that the paroxysm is reflexly terminated when the patient is able to bring up sputum that he has caused to form by the act of coughing.

An additional factor in many patients who suffer from paroxysmal cough without evidence of bronchial inflammation is the presence of edema of the lingual tonsils. These become quite large and impinge on the epiglottis, obliterating the vallecular space. The patient complains of a tickling or irritating sensation referred to the region of the jugular notch. He feels that there is something which he must bring up. The sensation is relieved when at last he brings up a tiny amount of sputum after a severe paroxysm of coughing.

It is possible, in these instances, that a small amount of secretion in the vallecular space may initiate the paroxysm because patients often state that a few sips of water will give them relief. However, it is unlikely that the ingested water does wash out the vallecula, since the space is reduced to a fine slit by the enlarged lingual tonsils. Just why a swallow of water should give temporary relief is not clear but it is probably due to some other cause than clearing of the vallecular space.

The edema of the lingual tonsils is largely due to the irritation of the cough itself. It completes a vicious cycle by causing a tendency to cough, while the cough perpetuates the edema of the lingual tonsils. We have found that this type of cough, which persists for weeks, months and even years in some individuals, is not apt to be controlled by codeine. We have been almost uniformly successful in stopping this type of cough within a day or two in the following manner:

The entire respiratory tract is examined most carefully, and, if nothing is found except the enlarged lingual tonsils, the patient should be reassured that he need have no fear of any disease in his lungs or bronchi. The mechanism of the vicious cycle is explained to him and he is told to make every effort to restrain his cough voluntarily. It is impressed upon him that the feeling of choking or irritation is caused by the edema of the lingual tonsils; that there is no secretion to be brought up, and that the secretion he finds is induced by the cough. He should, therefore, make no attempt to bring up sputum. If he feels that some secretion is present in his throat, he should swallow it and not try to expectorate. He should make no attempt at throat clearing since this also will tend to perpetuate the condition.

To help him refrain from coughing, I find it useful to prescribe a small dose of a barbiturate together with a small dose of codeine, to be taken frequently during the day, and to keep the medication and a glass of water at his bedside, ready to be taken immediately as the impulse to cough begins. It is suggested to him that the cough will be controlled by these measures within 48 hours and that the medication need not be taken for more than three days. It is literally amazing to note the sudden cessation of the paroxysms in a patient who has been distressed for weeks and months.

In some cases the above regimen is not entirely successful and in rare instances the cough cannot be controlled at all. The latter occurs particularly when the asset value of the cough is so great that the patient does not wish to be cured.

Such patients require expert psychiatric care. In others the condition is complicated either by an allergic state which perpetuates the lingual tonsil edema or a chronic sinusitis with a purulent postnasal drip which causes an infectious hypopharyngitis. If there is any evidence of an underlying allergic condition, an antihistamine should be prescribed at the first visit together with the other medication. If there is a purulent sinusitis, it should be brought under control before attempting to cure the cough.

By the use of these measures, practically all patients except the ones with severe psychoneurosis, can be rid of the paroxysms. Even in these, the attacks may be terminated by the application of Lugol's solution into the vallecular space. A large laryngeal swab is saturated with Lugol's solution. Under the guidance of a laryngeal mirror the swab is forced between the lingual tonsils and the epiglottis. A considerable amount of the Lugol's solution will be expressed from the swab into the vallecular space by a spastic contraction of the hypopharyngeal muscles. The solution is quite irritating for a period of fifteen minutes and may induce temporary laryngeal spasm and considerable anxiety on the part of the patient. However, it is frequently followed by complete cessation of the coughing attacks. Lugol's solution does serve to shrink the lingual tonsils and it may be that this is the reason for the beneficial effect. It is also quite possible that the relief is largely due to the distaste the patient has for the procedure and the fear that it may have to be repeated.

#### HEMOPTYSIS

While hemoptysis is always to be considered a danger signal of a serious organic disease, in roughly fifty per cent of the cases it proves to be relatively insignificant. In some, the bleeding occurs simply from dilated vessels in the bronchial mucous membrane. In others the origin is in the throat and is caused by the trauma of severe coughing. In the last instance, the cough responsible for the hemoptysis may be psychogenic.

When, in addition to the cough which perhaps has worried the patient for a considerable length of time, there is associated hemoptysis, the patient is apt to become alarmed. It may then be most difficult to persuade him that he is not suffering from a serious disease. Under these circumstances the cough may be intensified by the patient until he forces himself to bring up blood. His fear can usually be allayed by a careful explanation of the traumatic origin of the bleeding. He may be satisfied to accept the fact that the hemoptysis is no more serious than an ordinary nose bleed. One may then be successful in alleviating the cough as well as the hemoptysis.

More difficult to handle is the patient who brings up blood at will by suction on the gums or soft palate. The diagnosis of this type of induced hemoptysis is generally simple because the patient is usually able to bring up blood at any time. The suspicion that the blood originates in the mouth should be engendered if, on questioning, the patient states that the sputum is pink rather than red. The blood that is coughed up from the bronchi, trachea or larynx is bright red in color. That which is brought up from the mouth by suction action becomes mixed with

saliva. It is therefore pink and frothy. Given a history of the expectoration of pink or frothy bloody sputum in the absence of obvious pulmonary edema, one should always ask the patient to try to expectorate some blood. He will usually oblige because he has a desire to bring up blood. One can then note the sucking action by which it is produced.

It is remarkable that examination immediately after the expectoration of blood does not reveal a bleeding point in the gum or palate. However, the gums may appear spongy and sometimes dilated venules are seen on the soft palate or uvula.

The origin of the hemoptysis and its method of production should be explained to the patient. If he accepts the explanation he will generally stop making the sucking motion and be cured. If he refuses to accept the explanation, it is evident that he requires intensive psychiatric care.

In many instances hemoptysis originating in the bronchial mucous membrane is not associated with any important disease of the bronchi. This form of hemoptysis, which has been called benign bronchial bleeding or essential hemoptysis, occurs from dilated tiny vessels in the bronchial mucosa. In some cases the tendency to bleed is caused by hypertension or by dilatation of the bronchial vessels in mitral stenosis. In others, no underlying cause for the hemoptysis is evident.

Sometimes the cause of the hemoptysis lies in a diffuse dilatation of the blood vessels of the bronchial mucous membrane secondary to a disturbance of the vasomotor mechanism. This is probably the explanation for the hemoptysis which occurs repeatedly at the time of the menstrual period. Vasomotor instability, flushing and pallor, together with other manifestations of a disturbance of the sympathetic nervous system, are common during the menstrual cycle. It is fair to judge that this can occur in the bronchial mucous membrane as well as in other parts of the body.

Occasionally the hemoptysis occurs during a mild upper respiratory infection. Sometimes it follows a sense of irritation under the sternum lasting for as long as a day before the hemoptysis, suggesting a disturbance in the trachea. In one patient who had hemoptysis on several occasions during the menstrual period, I noted an unusual flush of the tracheal mucous membrane at about the time of the bronchial bleeding. The tracheal mucous membrane appeared normal between the menstrual periods but the congestion reappeared during subsequent menstrual periods even when she did not have hemoptysis.

Such erythema of the mucous membrane has been noted by others in patients with benign bronchial bleeding. Moreover, bronchoscopy at the time of a hemoptysis often reveals a rather characteristic tendency of the bronchial mucous membrane to bleed. During the bronchoscopic examination, the bronchial mucous membrane is seen to be diffusely congested even though there is no evidence of respiratory infection. Bleeding may be produced simply by touching the mucous membrane anywhere with an applicator. This tendency to capillary bleeding is not generalized and is unassociated with an increased bleeding time or a positive tourniquet test.

Several patients who have had repeated benign bronchial bleeding have told me that they could foretell the occurrence of hemoptysis for one or more days. During this time they experienced generalized flushing and uneasiness, and a sense of distress under the sternum. Whether these symptoms were the result of emotional influences which set off a train of events ending in bleeding is difficult to determine. However, their observations strongly suggest that the hemoptysis may be due to a functional disturbance of the blood vessels in the bronchial mucous membrane.

#### CHEST PAIN AND DISCOMFORT

Normally we are unaware of most of the stimuli, both exogenous and endogenous which are carried along the afferent pathways of our nervous system. The introspective or neurotic individual, however, feels many of these stimuli. If his neurosis is bound up with the region of the chest as a result of a past distressing experience, he will often complain of discomfort in the chest. Slight aching of the muscles which generally goes unnoticed may be magnified beyond the point of discomfort and reach the point of pain. This occurs particularly in hypersensitive individuals. Pain, therefore, must be evaluated in accordance to the sensitivity of the patient to painful stimuli. What may simply be a dull muscular ache in the average patient, may be magnified in a hypersensitive patient to the point of intolerance.

In considering the symptom of pain, it is wise to estimate the sensitivity of the individual. Most useful in this regard is the test devised by Dr. Emanuel Libman. He used the reaction of the patient to pressure over the styloid process of the temporal bone as an index of pain threshold. Moderate pressure on the styloid process, situated deep and anterior to the mastoid process, causes moderate pain in the average person. The hyposensitive individual complains only of a pressure sensation. If a patient thus found to be hyposensitive, complains of even a dull pain in the chest, the symptom must be taken seriously. On the other hand, the patient who winces, cries out or pulls his head away when only slight pressure is applied, is hypersensitive and his symptom of pain in the chest must be evaluated accordingly.

A common cause of chest pain is osteochondritis at the junction of one or more ribs with its cartilage. The pain is of a dull constant character, is rather persistent and associated with an extremely well localized point of tenderness at the costochondral junction involved. It is significant that the great majority of the cases of this type seen by the physician occur on the left side. The reason for this preponderance is apparent if one questions the patient. He will almost always say that the only reason he consulted a physician is that the pain is on the left side, that he is afraid it indicates heart disease and that he would not have gone to the physician if it had been on the right.

The patient can usually show the point of tenderness quite accurately because he has tested it. Not infrequently he will also state, on questioning, that when the pain has disappeared he searches for the tender point. After he finds it, the ache lasts for several days, and recurs each time after he re-examines



himself. It is understandable that he should do this when the condition is on the left side because he is worried about the possibility of heart disease. However, there is no question that the pressure of the finger on the area operates to perpetuate the tenderness. In this instance, therefore, there is a perpetuation of the osteochondritis by the trauma inflicted by the patient because of his mental reaction to the condition.

It is important to point this out to the patient if he is to get rid of his symptom quickly. It is also important to inform the patient that there may be an accentuation of the pain for several days as a result of palpation during the examination. It is good to point out that the condition is obviously a superficial one since the symptoms can be produced by pressure on the rib, and that the possibility of disease within the chest is excluded. This will usually be sufficient to permit the patient to forget about the condition, to make him refrain from further palpation, and thus put an end to the symptom.

#### HYPERVENTILATION SYNDROME

Rapid, deep breathing occurs as a physiological phenomenon in diabetic ketosis as a result of the acidosis. This is a normal response to the altered metabolic state. A similar change in respiration may occur in organic mental disease when there is no need for hyperventilation. We have observed it particularly in encephalitis, apparently from involvement of the respiratory center.

Hyperventilation occurs in even more severe form as an hysterical manifestation. The breathing is extremely deep and rapid, as in the performance of the test for maximum breathing capacity. After a period of hyperventilation, depending upon the rate and depth of respiration, alkalosis results. The patient experiences numbness and stiffness of the fingers and toes. This may be followed by typical carpopedal spasm and loss of consciousness. Even when the patient no longer seems able to respond, the hyperventilation continues. The attack is terminated when, as a result of washing out of carbon dioxide, a period of apnea sets in.

The psychic origin of this abnormality, as well as of some cases of bronchial asthma, is well illustrated by an observation in a patient who had severe asthma, and in whom no evidence of an allergic state or infection of the respiratory tract could be discovered. She was seen during an acute attack of asthma and given a fairly large dose of adrenalin. This promptly controlled all the evidences of bronchial spasm. Yet, the patient continued to breathe forcefully as if she still had asthma. Since the bronchial passages were then entirely free, the complete hyperventilation syndrome developed. The carpopedal spasm was controlled by having her rebreathe by means of a paper bag applied tightly over her nose and mouth. It was then suggested to her that there was no need for deep and rapid breathing. In response to this she quickly resumed normal respirations. This method may be used by the patient at home, after it has been impressed upon him that the treatment will control the tendency to rapid respiration. The employment of suggestion is necessary to insure success of the treatment.

## PSYCHIC INFLUENCES ON PULMONARY FUNCTION TESTS

It has been pointed out that motion of the diaphragm may be interfered with by psychic influences. This must be borne in mind in evaluating the results of spirometric pulmonary function tests in neurotic individuals. Certainly, an inhibition of the movement of the diaphragm or an alteration in diaphragmatic motion, brought on by the mental stress associated with the test, may result in diminution of the vital capacity. Similarly, failure to obtain the cooperation of the nervous patient can yield a low value for the maximum breathing capacity. These tests therefore, must be evaluated in relation to the mental condition and cooperation of the patient. In this respect the timed vital capacity may prove to be a more accurate determination of ventilatory function than the maximum breathing capacity in nervous patients.

False values of pulmonary function are often obtained in medicolegal cases, particularly in the nervous or hysterical individual who has been involved in an accident or exposed to an occupational hazard for which he claims damage to the respiratory tract. Such a patient may go through tremendous motions of respiration, using all the accessory muscles of respiration but not the basic ones, raising his chest but at the same time elevating his diaphragm so that little air enters the lungs. Under such circumstances a patient with normal respiratory function will perhaps show a vital capacity as low as 600 cc. Although this would suggest malingering, it is quite possible that the result may be entirely due to subconscious psychic factors. In such cases other tests which cannot be altered by the patient, such as the determination of the arterial blood oxygen saturation after exercise, may be required.

## PSYCHOTHERAPY

All patients displaying the functional disturbances which have been described require some sort of psychotherapy. In most of them the symptoms can be alleviated by reassurance from an understanding family physician. However, the patient must first be convinced that he is not suffering from a serious disease. Simply telling this to the patient is not sufficient to reassure him. He must be convinced that this case is taken seriously and that a thorough examination has been made by all the methods at the physician's command so that no important disease could be overlooked. This may require considerable time, effort and even expense to the patient. However, in the long run, less time will be consumed and less money expended if a complete examination is made initially.

It is most helpful to explain to the patient how all the methods of the examination have excluded serious organic disease, and the mechanism of the production of the symptoms should be made clear to him. How far one can go in this regard will depend upon the capacity of the patient to understand, but the goal should be to alleviate the anxiety concerning his complaints. Whereas the examination and explanation have their best effect when performed by one who is in a position of authority, such as the chest specialist, further reassurance, which may be required from time to time, had best be delegated to the family physician who knows the patient and in whom the patient has confidence.

It is generally considered undesirable for one not especially trained in psychiatry to probe into the psyche of the patient. I am heartily in agreement with this point of view. Such exploration by one who is not expert can bring to the surface conflicts producing additional symptoms, and may lead to incalculable harm.

If the symptoms do not respond rather promptly to reassurance and suggestive measures, expert psychiatric help should be sought. Whether this should be in the form of superficial or intensive psychotherapy had best be left to the discretion of the trained psychiatrist.

## FACTORS RELATED TO CHRONICITY OF LIVER DISEASE A PROGRESS REPORT

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The investigations of hepatic fibrosis carried out in the past years were continued with the use of routine light microscopy, electron microscopy, histochemistry, immunoocytochemistry, cytochemistry and chemical pathology. These studies were carried out on human material obtained by biopsy and autopsy and on serum, bile and tissues of rats in which various hepatic alterations were produced experimentally. These included acute fatty metamorphosis by short term administration of ethionine, acute hepatic necrosis with fatty metamorphosis by short term administration of carbon tetrachloride, chronic fatty metamorphosis with transition into cirrhosis by a high fat/low protein diet, chronic inflammation (hepatitis) with ductular proliferation by several weeks administration of ethionine, cirrhosis produced by long term administration of carbon tetrachloride, ethionine, 3'-methyl butter yellow, thioacetamide or N-2-fluorenyldiacetamide, formation of regenerative nodules without cirrhosis by long term administration of Aramite and dimethylnitrosamine, acute necrosis of bile duct epithelium with acute cholestasis by short term administration of alpha naphthylisothiocyanate, chronic portal fibrosis with ductular proliferation by chronic administration of alpha naphthylisothiocyanate, and acute extrahepatic biliary obstruction by ligation of the common duct.

In the study of hepatic fibrosis the problem of formation and of disappearance of collagenous fibers in the liver attracted the main attention with emphasis upon structural and functional features associated with these processes and possibly causally related to them. This broadened the problem of hepatic fibrosis into that of the causes of chronicity of liver diseases.

In the previous progress report, October 1958 to October 1959 (1), it was stated on the basis of light and electron microscopic studies that hepatic fibrogenesis is related to (a) alteration of liver cells, (b) proliferation of biliary ductules, and (c) portal inflammation (2). This was shown to be associated with activation of the hepatic reticuloendothelial cells reflected in periodic acid-Schiff reaction of their cytoplasm (3) presumably as a result of alteration of lysosomes (4), the cell organelles in the form of the dense bodies which contain hydrolytic enzymes, among them acid phosphatase. In the following, investigations are reported which are partly completed and partly in progress. Quotation is made of papers which have been submitted or have appeared since submission of the last progress report. Some of the papers quoted as appeared have

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been listed in the previous progress report as submitted. Much of the work is dovetailed with a study on correlation of structure and function in liver disease supported by the U.S. Public Health Service.

The investigations can be subdivided as follows: (A) mechanism of hepatic fibrosis and contribution of cells, (B) hepatocellular degeneration and its relation to fibrosis, (C) bile ductular proliferation and its relation to alteration of bile flow and to fibrosis, (D) relation of hepatic reticuloendothelial reaction to chronicity of liver disease, and (E) portal inflammatory reaction as exemplified by schistosomiasis.

#### A. MECHANISM OF HEPATIC FIBROSIS AND CONTRIBUTION OF CELLS

Subacute ethionine intoxication of rats served as a model for easily reproducible speedy formation of collagen fibers appearing under the light microscope mainly as reticulum. This was produced by administration of a diet containing 0.5 per cent ethionine. Within seven weeks, four to five times the pre-existing amount of collagen measured as hydroxyproline was present in the liver, the increase in the alkali soluble fraction being greater than in the insoluble fraction (5). In order to eliminate difficulties arising from interfering materials, a modification of the method for hydroxyproline determination was developed (6). The increase in hydroxyproline paralleled a similar four-fold increase of hepatic DNA content. The hydroxyproline/DNA ratio remained constant throughout the entire experiment. A similar constant ratio was found in other types of experimental hepatic fibrosis, as for instance that produced by a high fat/low protein diet, by administration of alpha naphthylisothiocyanate or by ligation of the common bile duct. In the case of the ethionine intoxication the parallel rise of the total hepatic DNA and hydroxyproline was accompanied by a two-fold increase of total hepatic protein and liver weight. This stimulated attempts at quantitation of the changes in the hepatic cell population during fibrogenesis. The quantitation was performed by differential cell counts according to Trowell and Westgarth. At the height of the fibrogenesis the total number of hepatic cells hardly changed while that of the mesenchymal cells doubled and that of the ductular cells increased fifty times. It appears thus that the new formation of ductular cells explains the increase in total hepatic protein during ethionine intoxication. Since light and electron microscopic investigations indicated that fiber-formation takes place at the outside of the basement membrane of the ductule in close approximation to neighboring mesenchymal cells, it was assumed that ductular cell proliferation acts as a stimulus for fibrogenesis, the proliferating ductules providing a mechanical scaffold (7). The intercellular substance appeared increased during fibrogenesis in this model experiment as well as in similar human and experimental examples. It gave reactions mainly for neutral mucopolysaccharides and less so for acid ones (3).

If following seven weeks of ethionine diet, a recovery diet supplemented with methionine or cortisone was given, hepatic protein, total hepatic DNA and total hepatic hydroxyproline dropped precipitously within two weeks, the hydroxyproline decrease being slightly less steep than that of DNA. Cell counts revealed

an almost normal cell population within two weeks. The remaining reticuloendothelial cells were rich in acid phosphatase and in a few instances fragments of collagen fibrils were seen in their cytoplasm under the electron microscope. Thus the liver is capable of catabolizing four to five times its normal collagen content within two weeks. From the experience gained so far, this "fibroclasia" seems to depend upon the presence of mesenchymal cells after the disappearance of the mechanical scaffold afforded by the ductular cells. The rapid catabolism of collagen in the recovery period following subacute ethionine intoxication is analogous to the rapid disappearance of fibers in cellular hepatic lesions in patients with subacute viral hepatitis or subacute alcoholic injury, in contrast to the persistence of fibers in acellular hepatic fibrosis (8).

To clarify further the fate and role of the disappearing cells, the life span of hepatic cells and of ductular cells is being estimated during the anabolic and catabolic phase, by autoradiography using tritiated thymidine for labeling newly developed cells. The effect of cortisone in the different stages of fibrosis is also controversial since it might influence both the fibroplastic as well as the "fibroclastic" cellular activity.

#### B. RELATION OF HEPATIC NECROSIS TO HEPATIC FIBROGENESIS AND CIRRHOSIS

In a light microscopic survey of a large number of necropsy cases of human cirrhosis, an attempt was made to differentiate four types of necrosis: (a) specific necrosis as an expression of the initial hepatic injury, for instance, Mallory's hyaline in alcoholics or single cell necrosis with acidophilic bodies in viral hepatitis; (b) ischemic necrosis in the center of lobules or nodules as a result of altered hepatic circulation and of anemia, usually found in patients with gastrointestinal hemorrhage; (c) biliary necrosis produced by intrahepatic disturbance of the bile flow; and (d) piecemeal necrosis associated with lymphoid and plasma cellular infiltration and usually with the local presence of gamma globulin (9) possibly an expression of self-perpetuation of the cirrhosis. All four forms of necrosis were found associated with fiber formation and several types contribute either simultaneously or consecutively to the cirrhotic transformation, exemplified in the cirrhosis of alcoholics (10). A similar survey of over 300 patients from various institutions revealed that in the presence of established alcoholic history, half of the cases were portal cirrhosis while in the other half features of postnecrotic cirrhosis (multilobular nodules, variation of nodular size and of regenerative activity throughout the nodule and broad areas of collapse) were found, although a grossly misshapen liver was never noted. In the absence of an alcoholic history, 7 per cent of the cases were postnecrotic cirrhosis, although only 10 per cent had a grossly misshapen liver. In the postnecrotic cirrhosis of alcoholics evidence of alcoholic hepatic injury such as fatty metamorphosis or alcoholic hyaline bodies of Mallory were frequent. This overlap of "alcoholic" and postnecrotic features were quantitatively estimated, and the presence of several stages in the same specimen verified. An evolution from portal cirrhosis with fatty metamorphosis of the alcoholic via necrosis, collapse and regeneration to postnecrotic cirrhosis as a terminal pathway was

postulated. It was assumed that the postnecrotic type of cirrhosis is that of the "reformed alcoholic" and that the increased frequency of postnecrotic features in recent years may reflect longer survival as a result of better management (9).

To study the relation between nodular regeneration and cirrhosis, hyperplastic nodules in the liver as produced by the drug Aramite were classified (11). Transition from such nodules in the absence of cirrhosis to hepatocellular carcinoma was demonstrated. Similar lesions were produced by other carcinogenic agents. Under these conditions excessive regenerative activity of the liver cells was associated with reduced reticulum stroma.

An attempt was made to define liver cell injury in man and in the experimental animal as an alteration of specific cell organelles. This study, still approached in this laboratory in a groping fashion, is particularly concerned with the recognition of alterations in viable rather than necrotic cells and is therefore carried out in the earlier stages of cellular involvement. Although clinical liver disease might be composed of initial alterations of several different organelles, rational therapy should ideally be directed against each type of initial insult. Injury to the endoplasmic reticulum, at present recognized as the site of protein and steroid synthesis and of detoxification, seems to occur characteristically in experimental injury from dimethylnitrosamine, in viral hepatitis and in some of the hepatic drug injuries in humans (12) which resemble viral hepatitis, as for instance, the hepatic injury resulting from administration of iproniazid (13). In contrast, most metabolic poisons seem initially to involve the mitochondria. In extrahepatic and intraphepatic cholestasis, characteristic alteration of the mitochondria were found. A particular abnormality of the mitochondria was noted in patients given various sulfonylurea derivatives particularly after chlorothiazide administration and independent of hepatic diseases. Such mitochondria were very large, had many cristae and a crystalline material seemed to be deposited in the mitochondrial substance. However, no correlation with altered hepatic function could be demonstrated. Acute ethionine intoxication was utilized to investigate the relation between mitochondrial injury and fatty metamorphosis. Various parameters of mitochondrial functions such as oxidative phosphorylation and the oxidation of Krebs cycle intermediates, amino acids and fatty acids were correlated with the hepatic fat concentration in ethionine intoxication as well as in its modification by cortisone, Janus green, dinitrophenol and methionine. The last has been shown to suppress the ductular cell reaction more than hepatocellular injury (14). Fat accumulation and mitochondrial damage occurred independently. The mitochondrial oxidation of fatty acids *in vitro* and *in vivo* as measured by isotope techniques using radioactive acetate or stearate was not impaired during hepatic fat accumulation and the specific activity of respiratory  $C^{14}O_2$  from these fatty acids was increased. Therefore, mitochondrial injury and fat accumulation are not necessarily related etiologically and the morphologically close association between mitochondria and fat droplets suggests a relative increase of energy provision by fatty acid oxidation (15).

As part of these investigations, a systematic survey of drug-induced jaundice

was performed (16, 17). Particularly, emphasis was being given to histochemical and electron microscopic alterations (18) and individual cases with liver injury produced by beta-phenylisopropylhydrazine (19) and chlorpropanide (20) were presented. Moreover, the enlargement of the liver as the result of excessive glycogen accumulation in diabetes was studied (21).

As the result of pioneer studies of deDuve and Novikoff, the importance of lysosomes as the site of various hydrolytic enzymes active in acid medium as well as the locations of various pigments were recognized. In this laboratory, disorders in which involvement of the lysosomes may be important are under investigation. Acid phosphatase has been localized by electron microscopy into lysosomes of the liver cells. A modified azo dye method for acid phosphatase activity is being utilized (22) as well as a modification of the beta glucuronidase method (23). The effect of different activators and inhibitors on the histochemical reaction of the specific phosphatases of liver was studied. These studies indicated the presence of at least four different ATPases, two 5-nucleotidases and one acid phosphatase demonstrable histochemically in formalin fixed frozen sections (24). Since abnormal lysosomes seem to give periodic acid-Schiff reaction, the reaction was subjected to further investigation (25) and quantitative analysis (26). As the result of light and electron microscopic investigations partly in agreement or confirmation of studies in Novikoff's laboratory, it appears that certain types of jaundice such as chronic idiopathic jaundice (of which biopsy specimens were available from two afflicted families (27)) are associated with specific alterations of the lysosomes possibly causing difficulties in transport of bilirubin through the liver cell. Moreover, this seems to be associated with alteration of the metabolism of lipofuscin. Its development under the light and electron microscope is under study and it appears that in some conditions its discharge into the bile is inhibited.

Changes of the lysosomes were also found in Wilson's disease. As the result of a light microscopic study of a large number of cases, a characteristic alteration was found, namely, a postnecrotic cirrhosis associated with small fat droplets in the liver cells, clumping of their cytoplasm and unusually heavy glycogen deposits in ballooned nuclei of the liver cells (28). On subsequent investigations on liver biopsy specimens with supplemental electron microscopy and histochemistry, a liver cell change was found in Wilson's disease which appeared fairly specific and characterized by an alteration of the lysosomes and deposition of an unusual pigment possibly accumulating by pinocytosis and of copper character (29). Massive necrosis of such cells in acute stages causes the postnecrotic cirrhosis. In iron storage diseases ferritin seems to be deposited in the lysosomes. They were subdivided on the basis of a light microscopic study into reticuloendothelial and parenchymal sideroses (30), the former being an expression of excess iron supply mainly from hemoglobin breakdown, the latter resulting either from genetic alterations or from increased transport of iron to the bone marrow under the influence of maturing red cells without adequate utilization by these cells. Severe parenchymal siderosis results in tissue alterations in the form of hemochromatosis.



The type of jaundice associated with alteration of the lysosomes and therefore with unusual distribution of the hepatocellular acid phosphatase has to be differentiated from intrahepatic cholestasis with dilated bile canaliculi containing bile plugs under the light microscope. This is characterized under the electron microscope by alteration of the biliary microvilli (31). This can be produced experimentally since patients and rats given norethandrolone in a dose known to reduce bromsulphalein retention showed dilatation of bile canaliculi with abnormal microvilli. This suggests that the cholestasis (32) produced by this drug results from a toxic action on the canalicular membrane (33). Investigations are underway by correlated light microscopy, electron microscopy and histochemistry with visualization of different phosphatase studies, to differentiate the mechanism of types of jaundice.

#### C. BILE DUCTULAR PROLIFERATION AND RELATION TO BILE FORMATION

Proliferated bile ductules in human and experimental animals differed under the electron microscope from liver cells by the appearance of cell organelles and the presence of a basement membrane. Since no transitional cells were noted, bile ductules did not seem to be derived from liver cells in postnatal life. The occurrence of microvilli in their lumen similar to that in the canalicular lumen of liver cells suggested a common function, probably regulation of the water content of the bile (34). The relation of the proliferated ductules to neighboring mesenchymal cells and to surrounding collagenous fibers suggested an irritating inflammatory role in addition to the mechanical scaffold role mentioned above. Apparently substances excreted in the bile in liver damage may have a growth stimulating effect on the ductules leading to their proliferation. For instance, carcinogens, such as Aramite in dogs, in whom the sphincter of Oddi produces stagnation of bile, caused carcinoma of the biliary ductal system or of the gallbladder (35). In addition, apparently an irritating material may be excreted leading to periductular inflammation and fibrosis. In proliferating ductules frequently PAS positive material, either polysaccharides or lipoproteins, was found. The ductular cell reaction seems therefore to represent a combined inflammatory and growth stimulating process.

To study the bile excretion in bile ductular proliferation, rate of bile flow, composition of bile and serum bilirubin were determined in rats during acute ethionine and carbon tetrachloride and during subacute ethionine intoxication. Only in the last injury which was characterized by extensive proliferation of ductules, the biliary excretion rose to four times normal. The rate of biliary solids increased while that of the bile acids decreased with reversal of the ratio between trihydroxy and dihydroxy bile acids and reduction of the bilirubin content as well as of rose bengal clearance. This indicated a hydrocholoretic effect and suggested that the microvilli of the ductules probably similar to the morphologically identical biliary microvilli of the liver cells reflect the excretion of an electrolyte containing fluid free of other biliary constituents comparable to the assumed function of similar ductules of the pancreas. To prove this duality of bile formation, investigations are planned in other intoxications with

bile ductular proliferation as well as of the effect of secretin and antidiuretic hormone upon hydrocholeresis. To study the role of lysosomes in biliary excretion, phosphatase activity in the bile was studied with the help of polyacrylamide gel electrophoresis which revealed three acid phosphatases in the rat liver (24).

To study the effect of intrahepatic biliary obstruction on bile stasis, alpha naphthylisothiocyanate was given in acute and chronic experiments. Single doses have been shown by Israeli observers to produce intrahepatic biliary obstruction by necrosis of the epithelium of the bile ducts. Chronic feeding has been described by Italian and British investigators to be associated with severe ductular proliferation apparently as a result of the initial necrosis. In this laboratory complete cessation of bile flow with deep jaundice was observed in the acute stage while in the chronic stage in the absence of jaundice the bile flow was four times normal and gradually fell to twice normal.

#### D. RELATION OF HEPATIC RETICULOENDOTHELIAL REACTION TO CHRONICITY IN LIVER DISEASE

Increased activity of the hepatic reticuloendothelial cells as well as those of lymph node and spleen was reflected in increased nonglycogenic PAS positive material in the cytoplasm as well as by high activities of acid phosphatase. The latter was studied in these organs by both histochemical and chemical methods to permit quantitation (36). PAS reaction and acid phosphatase activity indicate phagosomes (the lysosomes of reticuloendothelial cells).

Gamma globulin was demonstrated particularly in hepatitis and postnecrotic cirrhosis in mesenchymal cells of plasmacytoid character within the lobular parenchyma and within the portal tracts in active hepatitis and postnecrotic cirrhosis (37). These studies have been extended in part by using simple methods for the processing of tissues for immunocytochemical studies particularly of liver biopsy specimens. One is brief fixation in buffered cold formalin and the second freeze substitution, both subsequently followed by paraffin embedding. This results in technically much better sections than those cut with the cryostat. In a patient with Waldenstroem's macroglobulinemia who developed serum hepatitis, the reticuloendothelial cells of the liver did not contain the usually found 7S gamma globulin but rather 19S macroglobulins indicated by studies with appropriate antisera for immunocytochemistry. Further studies of the nature of the gamma globulin fluorescence using various antisera and by elution techniques indicated that in postnecrotic and diffuse septal cirrhosis only gamma globulin and no albumin or fibrinogen is demonstrable in the mesenchymal cells. In acute viral hepatitis the reticuloendothelial cells contain such serum proteins. This suggests that in cirrhosis, gamma globulin is not present as a result of phagocytosis, but rather, formed locally. The gamma globulin demonstrable in the liver is not eluted at a pH of 3.2 indicating that it is not bound to antigens.

The investigations so far do not preclude the possibility that the local presence of gamma globulin in cirrhosis reflects an immunologic reaction. To further

investigate this possibility, immunocytochemical techniques were used to determine whether sera of patients with liver disease contain iso- or auto-antibodies to normal or abnormal liver tissue. In only a few instances was binding to either liver cell nuclei or to cytoplasm of ductular cells found. Additional studies are required definitely to establish to what degree and in what condition immunologic processes contribute to the self-perpetuation of liver disease.

To study serum protein changes in liver disease, polyacrylamide gel electrophoresis was employed. A slow moving protein possibly gamma globulin band was reduced in patients with cholestasis and increased in those with predominant liver cell damage. The reverse was true with a faster moving band. In all patients with liver cell damage even when associated with cholestasis, the gamma globulin bands tended to be blurred.

#### E. PORTAL INFLAMMATORY REACTION AS EXEMPLIFIED BY SCHISTOSOMIASIS

The pathologic features of human schistosomiasis were studied (38). In this condition increased splenic pressure coincided with a normal hepatic vein wedged pressure indicating presinusoidal localization of the portal hypertension (39). To clarify further the pathogenesis of the hepatic alterations in this disorder, vascular lesions of mice infected with *schistosoma Mansoni* were studied in livers injected with india ink *in vivo* and postmortally. Endovascular granulomas occluded terminal portal venules, explaining the portal hypertension. The parenchyma distal to such obstructed venules was supplied by pre-existing collateral channels while arteriovenous shunts were not observed (40).

#### SUMMARY

Hepatic fibrosis and associated features related to causes of chronicity of liver disease were studied with light microscopy, histochemistry, electron microscopy, immunochemistry, cytochemistry and chemical pathology in human and experimental material. In investigating the mechanism of hepatic fibrogenesis and the contribution of cells, experimental ethionine intoxication of the rat served as a model; rapid fiber formation was associated with increased numbers of cells reflected in parallel rise of hepatic DNA. Some of these cells were mesenchymal but the majority were biliary ductules which seemed to serve as a mechanical scaffold for the developing fibers. In the recovery period the liver catabolized four times its normal collagen content within two weeks. This appeared to be related to the cellularity of the lesion, and a fibroelastic activity of the mesenchymal cells was postulated. Various types of hepatocellular degeneration related to fiber formation were distinguished by either etiologic factors or involvement of specific organelles of the hepatic cells. Various injurious agents initially afflicted different cell organelles. This also permitted differentiation of several types of jaundice. Fat accumulation in ethionine intoxication was found to be unrelated to mitochondrial injury. In alcoholics the frequent occurrence of postnecrotic cirrhosis was demonstrated; it resulted from a transition from diffuse portal cirrhosis via necrosis, collapse and regeneration, apparently facilitated by prolongation of life. Bile ductular proliferation and

periductular inflammation were considered to be the result of the excretion of growth stimulating as well as irritating factor which stimulate fibrosis. It was associated with hydrocholeresis. Dual biliary excretion was postulated in that through the microvilli of ductules and liver cells an electrolyte containing fluid free of biliary constituents was secreted. Activation of the reticuloendothelial cells of the liver demonstrated by various methods was associated with gamma globulin formation by these cells in hepatitis and cirrhosis. To what degree this represented an autoimmune reaction related to self-perpetuation of the cirrhotic process remains to be proved. Occlusion of terminal portal venules explained the portal hypertension in schistosomiasis.

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## ENZYMATIC PATTERNS IN DEMYELINATION

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If one surveys the attempts to produce conditions analogous to multiple sclerosis experimentally in animals, one finds that the phenomenon of Wallerian degeneration provides an easily available model for demyelination in spite of the obvious differences in the area affected. Waller, more than 100 years ago, observed that the excision of a section of peripheral nerve will lead to degeneration of the distal stump. The myelin sheath dwindles, while macrophages infiltrate and Schwann cells proliferate. Comparisons have been reported in the literature of the enzyme content of the distal stump with that of normal nervous tissues. Heinzen has reported an increase in acid pH phosphatase in Wallerian degeneration (1). Lumsden in Glick's laboratory has observed a significant drop in esterase (2). Hollinger *et al.* described a 30 to 40-fold increase in  $\beta$ -glucuronidase activity in sciatic nerve degeneration in the cat (3). Porcellati and Curti showed a 150 per cent increase of proteinase (pH 7.4) after nerve section (4). McCaman and Robins studied 12 enzymes in Wallerian degeneration of the sciatic and the optic nerve in rabbits (5). Except for the last named authors, the observations showed a maximal effect one to four weeks after transection.

The correlation of these changes in enzymatic patterns with the metabolic events in degeneration are not easily understood. The significance of esterases and phosphatases for the metabolism of lipids, a dominant constituent of neural tissue, and of nucleotidases appears to be quite plausible. The significance of the presence and of the changes in  $\beta$ -glucuronidase, cytochrome oxidase and the various glycolytic enzymes requires more sophisticated reasoning.

One may look for correspondence between the enzymatic findings and the cellular changes. The enzymes studied fall into two groups: one showing signal increases, the other group characteristic diminution. Could these two contrasting groups be correlated with the proliferation of the Schwann cells and the infiltration of macrophages and, on the other hand, with demyelination? (Alteration of the water content of the tissue upon transection must also be taken into account).

In the following we report observations and changes of phosphatases, also of 5-adenosinase and of  $\beta$ -glucuronidase in the course of Wallerian degeneration, subsequent to transection and excision of the sciatic nerve in adult rabbits. Both the excised portion (E) and, after sacrifice of the animal, the contralateral sciatic nerve (C) served as control tissue.

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This research was supported by Grant No. 248R of the National Multiple Sclerosis Society, by U.S. Public Health Service Grant No. B-1935, and by a Grant from the National Association for Mental Health.

## SURGICAL PROCEDURE

Male rabbits 3–5 kg were anesthetized with Nembutal under sterile conditions. An incision was made over the proterolateral aspect of the thigh. The gluteus maximus was divided and the sciatic nerve exposed. The nerve was transected about 3–4 cm distal to its emergence from the spinal canal, and a 1 cm segment was excised. Bleeding was negligible and the wound was closed in layers. Each animal received 300,000 units of Bicillin preoperatively.

## COLLECTION OF TISSUE

The experiments were terminated after 1 to 4 weeks by sacrificing the animal with an intravenous lethal dose of Nembutal and the operated nerve trunk, distal to the transection, was dissected for a length of 5–6 cm. This segment was divided into three portions of 1–2 cm length ( $D_1$ ,  $D_2$ ,  $D_3$ ). The corresponding portion of the contralateral nerve (C) was removed as control. Each segment was bisected lengthwise; one part was used for chemical, the other for histochemical and histological studies.

## ENZYMATIC METHODS

The following substrates were incubated with homogenized nerve tissue, corresponding to 2 mg of fresh tissue, for 24 hours at 37.5°. Acid phosphatase was determined with  $C_6H_5OPO(ONa)_2$  in citrate buffer of pH 4.9. Adenosinase was determined with adenosyl-5-phosphate as substrate in acetate buffer of pH 4.8. Glucuronidase was determined with phenolphthalein glucuronide in acetate buffer of pH 4.5. The turnover was kept within 10 per cent of the theoretically possible.

## HISTOLOGICAL TECHNIQUE

The segments for the histological study were fixed in cold (4°) 4 per cent neutral formol-calcium for 24 hours. Histochemical procedures were performed on frozen sections. Additional segments of the fixed block were dehydrated, embedded in paraffin and sectioned at 4–6  $\mu$  for routine staining purposes. Staining procedures included hematoxylin and eosin, periodic acid-Schiff reaction, Mahon technique for myelin, Holmes procedure for axons, Sudan black or Oil red O in triethylphosphate for lipids. Acid phosphatase activity was demonstrated by the hexazonium pararosaniline technique of Barka (6). Esterase activity at pH 7.3 was visualized by the method of Davis and Ornstein (7).

## RESULTS

The animals fall into three groups. Group I received no treatment. Since the enzymatic determination deviated strikingly from normal in the demyelinating tissue, we set out to determine the origin of the increased enzyme titers. This could result from: 1) accumulation of macrophages; 2) proliferation of Schwann cells; or 3) combined activity of both cell types. To test the possible influence of corticosteroids on the histiocyte response, we treated Group II daily with cortisone, 1 mg per kg intramuscularly, for the duration of the experiment.

Penicillin was also administered during the postoperative period to eliminate wound infection. An attempt was also made to influence macrophage activity with Thorotrast by injecting Group III with 25 per cent of ThO<sub>2</sub> suspension (Thorotrast). The animals received from 1 to 7 intravenous injections of 9 ml each between operation and sacrifice. Initial dose was administered one day prior to operation.

#### HISTOLOGICAL OBSERVATIONS

In all operated nerves severe progressive degeneration was evident histologically. Demyelination was always accompanied by a pronounced increase in macrophages along the degenerating fiber. There was also considerable proliferation of Schwann cells. A conspicuous increase in histochemically demonstrated acid phosphatase activity was observed in both Schwann cells and macrophages. These changes increased in severity depending on time of degeneration. This pattern of degeneration was not altered in animals treated with cortisone and Thorotrast. No significant difference in macrophage population could be detected in these animals compared to the untreated controls.

The livers and spleens of animals that had received Thorotrast, however, showed a remarkable increase in size (3 to 10-fold). Histologically, these organs showed numerous focal aggregates of conspicuously enlarged Thorotrast-laden histiocytes. These histiocytes also exhibited intense histochemical staining for acid phosphatase activity.

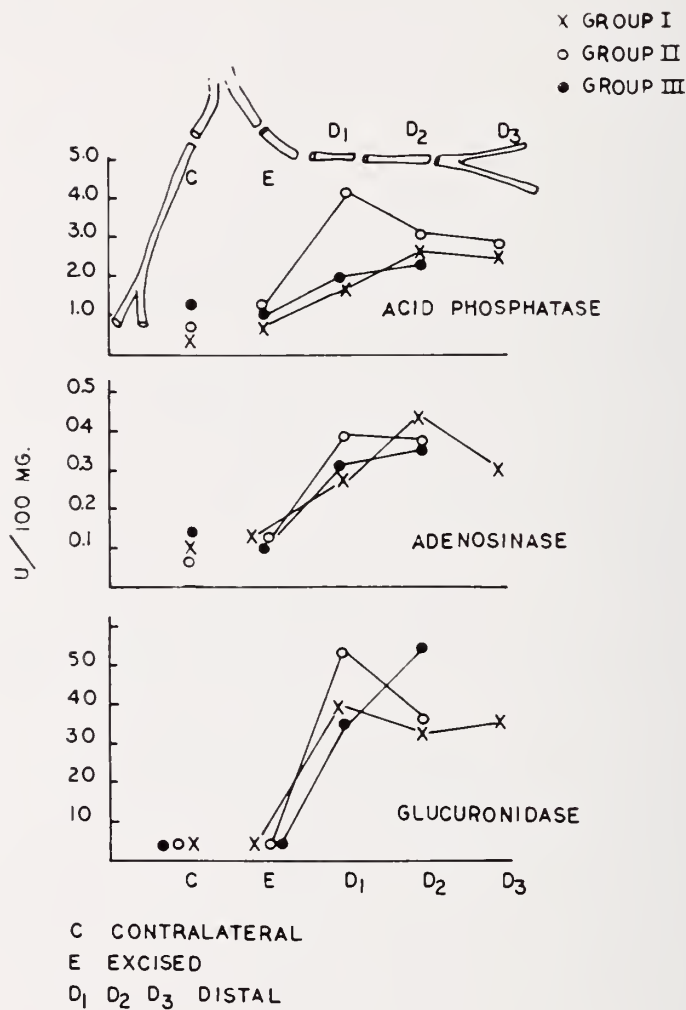
#### ENZYMATIC OBSERVATIONS

The graphs illustrate the average values obtained for the three groups. The units are given per 100 mg of wet tissue for a reaction time of 24 hours; only in the case of glucuronidase are they calculated for one hour periods. The points on the left side are the values of the contralateral sciaticus at time of sacrifice. The curve reading from left to right indicates the enzymatic titer of the excised nerve tissue at the time of excision; the 2 or 3 values to the right refer to the values in sections of the distal stump at the time the animal was sacrificed. These values comprise the average of animals sacrificed at different periods (1 to 5 weeks). All three enzymes studied are increased in various portions of the distal stump. The increase is up to 5-fold (maximum) with 4-fold (average) for acid phosphatase. For adenosinase it is 7-fold (maximum) and 4-fold (average). For glucuronidase it is 18 times (maximum) and 10 times (average).

Substantially increased enzyme titers were observed after one and two weeks as well as after longer periods. No uniform trend with time could be observed. As each animal provides one specimen beside the starting point, the statistical treatment of the data must take into consideration the biological variation from one rabbit to another, based on age and other factors not germane to the problem. The control values of the excised portions vary up to  $\pm 25$  per cent of the average. The contralateral controls likewise vary, in a few instances even beyond this range, possibly due to systemic reactions to the operation. For this reason we have averaged the values from operated animals without subdivision as to periods.



Our studies show that the hydrolases under consideration increase 4 to 10 times on the average in Wallerian degeneration of the rabbit's sciaticus. In a search for the kind of cell to which these increases may be ascribed, we have not



for enzyme units see text

FIG. 1. Enzymatic Patterns in Demyelination in Wallerian Degeneration of the Sciatic Nerve in Rabbits.

been able to modify macrophage activity with either cortisone or Thorotrast. Extensive histological studies show no difference in the quantity and quality of the cellular population in the peripheral tissue between treated and untreated animals. The amounts of Thorotrast used were at the upper limit of the tolerated range and produced extreme effects in the visceral organs.

During the course of degeneration of peripheral nerve, Schwann cells undergo considerable morphologic change. Accumulation of lipid debris in their cytoplasm suggests that these cells may engage in phagocytic activities. The swollen cell finally appears indistinguishable from enlarged debris-laden macrophages. It is probable that the enzymatic changes observed in Wallerian degeneration are a reflection of changes in activity of both, Schwann cells and macrophages.

#### ALKALINE PHOSPHATASE

We have also performed a few preliminary determinations of the alkaline phosphatase which suggest that this enzyme like Lumsden's esterase is rather diminished in Wallerian degeneration. In the course of these experiments we observed that carbonate-bicarbonate buffer at pH 10.0 inhibits the phosphatase in contrast to the glycine buffer at the same pH. This inhibitory effect is even shown by the addition of as little as 0.02 M carbonate-bicarbonate to glycine buffer experiments. This effect appears to be specific for the phosphatase of peripheral nerve tissue.

#### SUMMARY

We have developed a coordinated set of surgical, histological and enzymatic procedures for the study of Wallerian degeneration. Using excision of the rabbit's sciatic nerve we find substantial increases of several hydrolases in the degenerating nerve. Treatment of the animals with cortisone or Thorotrast did not affect the enzymatic activity or histologic appearance of the operated nerve.

Alkaline phosphatase belongs to a second group of enzymes which are found diminished in demyelination. This enzyme was observed to be specifically inhibited by small amounts of carbonate.

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## SOCIAL AND FUNCTIONAL REHABILITATION OF PATIENTS WITH SEVERE POLIOMYELITIS\*

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### INTRODUCTION

Rehabilitation programs in general provide gratifying results for the patient group with severe physical involvement, even though most of the patients remain with mild to moderate generalized disability or a severe localized deficiency.

Catastrophic illnesses characterized by severe and extensive residua still present perplexing and frustrating problems for the achievement of physical rehabilitation, as well as social, emotional, and community reorientation. The establishment of respirator care and rehabilitation centers by The National Foundation has offered an opportunity for the study, development, and application of improved techniques to this extremely challenging problem.

### BACKGROUND

The following material represents the results of six and one-half years experience at the Jack Martin Poliomyelitis Clinical Study Center of the Mount Sinai Hospital. The unit, established in October of 1953 under the joint auspices of The Mount Sinai Hospital and The National Foundation, was a 17-bed facility for the care of poliomyelitis patients with respiratory difficulties. In order to provide comprehensive medical care, a treatment team composed of members representing ten disciplines was brought together. A medical director was generally responsible for the program and its coordination. It was believed that this position should be held by a physician with rather broad medical interests as well as a good experience in the field of poliomyelitis. For these and other local reasons a pediatrician was in charge of this unit. In addition, there was a psychiatrist, a physiatrist, an orthopedist, and a urologist. To complete the group, there was an experienced social worker who was versed in rehabilitation, psychiatry and general medicine, a group of specially trained nurses, occupational therapists, and physical therapists. Of course, members of virtually every department in this large general hospital participated to some degree at one time or another.

The requisite for admission was the patient's continued respiratory inadequacy resulting from poliomyelitis beyond the acute phase of the disease. Patients were admitted in order of referral, although occasionally an emergent case would be given preference. No patient was denied admission because of the degree of paralysis or medical or social complications.

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During the period of this experience, 125 patients were admitted to the unit. Of these, 90 were poliomyelitis patients with respiratory inadequacy who had been hospitalized elsewhere during the acute phase of their illness and for a variable period thereafter while awaiting admission to this center. Four of these have been discharged too recently to warrant inclusion in this study. Of the remaining 35 patients, 7 did not have poliomyelitis, 3 had acute poliomyelitis without respiratory problems and 25 were chronic poliomyelitis patients of long-standing who were admitted for short-term evaluation and/or for treatment of an intercurrent illness. This study will be concerned with the 86 so-called chronic poliomyelitis patients who, during their hospitalization or thereafter, required the use of respirators of one kind or another (tank respirators, cuirass respirators, rocking beds, positive pressure respirators, etc.).

The patient population presented here has been grouped according to whether respiratory aids were or were not necessary at the time of discharge. Further, the members of each of these groups were classified into categories as follows:

- I. Quadriplegics
  - A. Nonfunctional
  - B. Minimally functional
  - C. Moderately functional
- II. Paraplegics
  - A. Functional upper extremities
  - B. Functional lower extremities
- III. Functional with generalized weakness

Those indicated as being quadriplegic and nonfunctional were completely paralyzed below the neck. The quadriplegics who were minimally functional were able to perform but little upper extremity activity with or without mechanical assistance. The moderately functional quadriplegics had fair upper extremity function with or without mechanical devices. Those classified as functional with generalized weakness were able to do light work with their upper extremities and to ambulate with limitations. However, two patients in this category regained grossly complete recovery although there was an occasional weak muscle.

For purposes of discussion, the patients have been classified in three categories from the standpoint of vocational rehabilitation. Those who were completely nonfunctional are referred to as vocationally nonproductive [O]. Partial vocational rehabilitation [P] indicates that the patient is productive vocationally and economically but below his or her pre-illness level. Total vocational rehabilitation [T] indicates productivity and remunerative work at or above the pre-illness level.

## RESULTS

### *Respirator Patients*

Quadriplegic; nonfunctional [I-A].

In this category, there are 30 patients (Table I). All were discharged to their homes except for 2 who died and 10 who were transferred to other institutions



for chronic care. Of the remaining 18 patients, 9 (30 per cent of all patients in this group) are at home and are classified as vocationally nonproductive. Seven (23 per cent) have returned home and are partially vocationally rehabilitated. Two (7 per cent) have returned to their families and are totally vocationally rehabilitated in spite of the need for respiratory assistance and their severe and extensive paralysis.

TABLE I  
*Vocational Attainment of 86 Poliomyelitis Patients According to Degree of Paralysis and Need for Respiratory Assistance*

		I			II		III	Total
		QUADRIPLÉGIC			PARAPLÉGIC		Functional with Gen'lized Weakness	
		A	B	C	A	B		
		Non-functional	Minimally Functional	Moderately Functional	Functional Upper Extremities	Functional Lower Extremities		
Respiratory	O	21	3	0	1	0	0	25
	P	7	13	0	0	2	0	22
	T	2	3	4	1	2	1	13
	Total	30	19	4	2	4	1	60
Non-Respiratory	O	0	0	0	1	0	0	1
	P	2	3	1	3	0	0	9
	T	0	0	0	7	2	7	16
	Total	2	3	1	11	2	7	26
Grand Total		32	22	5	13	6	8	86

O—Vocationally nonproductive.

P—Partially vocationally rehabilitated (below pre-illness level).

T—Totally vocationally rehabilitated.

Quadriplegic; minimally functional [I-B].

Nineteen patients are classified in this group (Table I). They were all discharged to their homes. Only 3 (16 per cent) are considered to be vocationally nonproductive while 13 (68 per cent) are partially vocationally rehabilitated. Even with widespread limitations imposed by the disease, 3 patients (16 per cent) in this group are totally vocationally rehabilitated.

Quadriplegic; moderately functional [I-C].

Only 4 members comprise this group of patients who are dependent to some degree upon mechanical respiratory assistance and have moderate upper extremity function (Table I). Nevertheless, all of these patients are totally vocationally rehabilitated.

Paraplegic with upper extremity function [II-A].

Only 2 patients comprise this group (Table I). One died of renal failure. The other is totally vocationally rehabilitated and living at home with his family.

Paraplegic with lower extremity function [II-B].

There are 4 patients in this group of individuals who can walk but are without upper extremity function or freedom from respiratory assistance (Table I). Two are partially and 2 are totally vocationally rehabilitated.

Functional with generalized weakness [III].

Only 1 patient comes within this classification. He is a school-age child who uses a tank respirator at home during sleep but attends a school for handicapped children during the day (Table I).

#### *Non-Respirator Patients*

Quadriplegic; nonfunctional [I-A].

Two patients are in this group and both are partially vocationally rehabilitated in spite of their total lack of function below the neck (Table I).

Quadriplegic; minimal function [I-B].

In this group, there are 3 members all of whom are partially vocationally rehabilitated (Table I).

Quadriplegic; moderate function [I-C].

One patient makes up this group and he is partially vocationally rehabilitated (Table I).

Paraplegic with upper extremity function [II-A].

Of 11 patients who comprise this group, 3 are partially vocationally rehabilitated while 7 are totally vocationally rehabilitated. One patient is not productive (Table I).

Paraplegic with lower extremity function [II-B].

The 2 patients who have well functioning lower extremities are totally vocationally rehabilitated although upper extremity function is ineffectual (Table I).

Functional with generalized weakness [III].

This group is made up of 7 patients, all of whom are totally vocationally rehabilitated (Table I).

Of the 59 quadriplegic patients, 2 died and 10 were transferred elsewhere for chronic care. Of the remaining 47 patients, 30, or half of this severely involved group, are partially or totally rehabilitated although 25 or 83 per cent have respiratory inadequacy sufficient to require the use of mechanical breathing aids.

As one might expect, the majority of patients who have not realized vocational

rehabilitation are of the quadriplegic type. Eighty-six patients comprise the entire study group and of that number vocational rehabilitation was not attained in 26 of whom 24 were quadriplegic (2 dead, 10 institutionalized, 12 discharged to their homes).

The paraplegic patients have been remarkably successful in attaining vocational rehabilitation whether or not respiratory assistance is needed. Twenty-five of 27 paraplegics were totally (20) or partially (5) vocationally rehabilitated. Of the remaining 2, 1 who had very good physical potential for vocational

TABLE II  
*Vocational Attainment of 39 Male Adult Poliomyelitis Patients According to Degree of Paralysis and Need for Respiratory Assistance*

		I			II		III	Total
		Quadriplegic			Paraplegic		Functional with Gen'lized Weakness	
		A	B	C	A	B		
		Non-functional	Minimally Functional	Moderately Functional	Functional Upper Extremities	Functional Lower Extremities		
Respiratory	O	11	2	0	1	0	0	14
	P	2	2	0	0	1	0	5
	T	2	2	4	1	1	0	10
	Total	15	6	4	2	2	0	29
Non-Respiratory	O	0	0	0	1	0	0	1
	P	1	0	0	1	0	0	2
	T	0	0	0	2	1	4	7
	Total	1	0	0	4	1	4	10
Grand Total		16	6	4	6	3	4	39

O—Vocationally nonproductive.

P—Partially vocationally rehabilitated (below pre-illness level).

T—Totally vocationally rehabilitated.

rehabilitation but a severe pre-illness personality problem committed suicide following discharge, and the program of the other has been obstructed by his psychotic mother.

Of course, vocational goals vary with age, sex, and pre-illness training and experience. Accordingly, it seemed appropriate to assess each patient's vocational achievement on the basis of his or her own pre-illness social and vocational roles. For example, the women are considered to have achieved vocational rehabilitation when their pre-illness role of housewife and mother was realized.

For simplification, it seemed appropriate to consider the results according to whether the patients were men, women or children (Tables II-IV). No sex distinction was made in the children's group.

There are 39 men in the study (Table II) of which 29 were using respiratory aids at the time of discharge. Fifteen of these are quadriplegic and are considered to be nonfunctional. Eleven attained no vocational rehabilitation; 5, because of inadequate home situations, were transferred to other institutions for chronic care. Two are partially and 2 are totally rehabilitated. Six patients dependent upon respiratory assistance are classified as quadriplegic with minimal upper extremity function and are equally divided among the various categories in vo-

TABLE III

*Vocational Attainment of 39 Female Adult Poliomyelitis Patients According to Degree of Paralysis and Need for Respiratory Assistance*

		I			II		III	Total
		Quadriplegic			Paraplegic		Functional with Generalized Weakness	
		A	B	C	A	B		
		Non-functional	Minimally Functional	Moderately Functional	Functional Upper Extremities	Functional Lower Extremities		
Respiratory	O	10	1	0	0	0	0	11
	P	5	9	0	0	1	0	15
	T	0	1	0	0	1	0	2
	Total	15	11	0	0	2	0	28
Non-Respiratory	O	0	0	0	0	0	0	0
	P	0	0	0	2	0	0	2
	T	0	0	0	5	1	3	9
	Total	0	0	0	7	1	3	11
Grand Total		15	11	0	7	3	3	39

O—Vocationally nonproductive.

P—Partially vocationally rehabilitated (below pre-illness level).

T—Totally vocationally rehabilitated.

ational rehabilitation. Four men still using respiratory assistance who are quadriplegic with moderate upper extremity function are totally rehabilitated.

In the respiratory group, there are 2 paraplegic men with upper extremity function. One died and the other attained total vocational rehabilitation. Of the 2 with lower extremity function, 1 attained partial and the other total rehabilitation. Ten men were discharged without the use of respiratory assistance. One is a nonfunctioning quadriplegic who has become partially vocationally rehabilitated. There are 4 men in this category who are paraplegic with upper extremity function. One achieved virtually no vocational rehabilitation, 1 is partially rehabilitated and 2 are totally rehabilitated. One paraplegic with lower extremity function is totally rehabilitated. Four men with residual generalized weakness attained total vocational rehabilitation.



Of the 39 women in this study (Table III), 28 have respiratory inadequacy. There are 15 women using respiratory aids who are quadriplegic and nonfunctional. Ten are considered to be not vocationally rehabilitated. Of these ten, 5 were transferred to other institutions for chronic care because of inadequate home situations. Two died in the center. Only 3 women from this group then returned to their homes without attaining some degree of rehabilitation, despite their severe involvement. There are 11 quadriplegic women with minimal upper

TABLE IV  
*Vocational Attainment of 8 Child Poliomyelitis Patients According to Degree of Paralysis and Need for Respiratory Assistance*

		I			II		III	Total
		Quadriplegic			Paraplegic		Functional with Gen'lized Weakness	
		A	B	C	A	B		
		Non-functional	Minimally Functional	Moderately Functional	Functional Upper Extremities	Functional Lower Extremities		
Respiratory	O	0	0	0	0	0	0	0
	P	0	2	0	0	0	0	2
	T	0	0	0	0	0	1	1
	Total	0	2	0	0	0	1	3
Non-Respiratory	O	0	0	0	0	0	0	0
	P	1	3	1	0	0	0	5
	T	0	0	0	0	0	0	0
	Total	1	3	1	0	0	0	5
Grand Total		1	5	1	0	0	1	8

O—Vocationally nonproductive.

P—Partially vocationally rehabilitated (below pre-illness level).

T—Totally vocationally rehabilitated.

extremity function and respiratory dependency and only 1 has not attained an appreciable degree of rehabilitation. However, 9 are partially and 1 is totally vocationally rehabilitated. Of the 2 remaining women in the respiratory group, both are paraplegic with lower extremity function. One has attained total vocational rehabilitation and the other is partially so.

Eleven women were discharged free of respiratory devices, none of these are quadriplegic. Seven are paraplegic with upper extremity function. Of these, 2 are partially vocationally rehabilitated and 5 are totally vocationally rehabilitated. One with lower extremity function is totally rehabilitated. Of the remaining 3 female patients, all attained total vocational rehabilitation.

In the entire group of 86 patients there are 8 children (Table IV). Of these,

3 were still using respiratory aids at the time of discharge. Two of these children are quadriplegic with minimal upper extremity function. Because they have continued their schooling with home instruction, they are considered partially rehabilitated. One child who sleeps in a tank respirator at home is considered totally rehabilitated because he attends a school for physically handicapped children. Five children require no respiratory assistance and fall within the quadriplegic group. They all continue to receive school instruction at home and are therefore considered partially vocationally rehabilitated.

#### DISCUSSION

Much has been written about the medical care of patients with acute poliomyelitis as well as the treatment of after-effects, particularly respiratory insufficiency and renal complications. Symposia, clinics and workshops have been held to teach modalities and techniques to physical and occupational therapists. Similar efforts have been made in teaching the nursing aspects of poliomyelitis. Consequently, noteworthy advances have been made in the medical and surgical management of poliomyelitis patients. Unfortunately, relatively little attention has been directed to the practical and realistic utilization and application of the fine physical results which these efforts have produced. The sustained effort, excellent technical skills and considerable time expended in the care of these patients are imperative and their importance is unquestioned, but their yield falls short if the paramedical disciplines do not function with equal vigor and effectiveness. It is to this aspect of the aftercare of poliomyelitis that this communication is directed.

In reviewing our results it becomes evident that despite the degree of physical involvement, the patient who was formerly presumed to need custodial care can, by modern medical and social techniques, be returned to his home and community as a functioning individual.

The goal set for each patient is maximum rehabilitation within his own limitations. However, it must be made clear that the limitations are not only physical, but social and emotional as well. It is not uncommon that a patient with extensive physical involvement makes a better adjustment to his illness, vocationally and socially, than another patient with less physical involvement.

Treatment of a catastrophic illness requires long hospitalization; yet, when one considers the extent of physical and emotional regression and the necessary investment made by both patient and staff to achieve emotional and physical restoration, this period is all too short. Assessment of the patient and establishment of goals must therefore be started early and the patient's treatment program must be well planned and purposefully followed. Discharge planning actually begins on admission.

In order to achieve maximum rehabilitation for the patient socially and vocationally, since one cannot be separated from the other, it must be known what the patient was like prior to his illness; how he functioned in his environment relative to his family members, his community, and employment; and his present feelings toward his illness, his future, and his physical limitations. Each pa-

tient brings to his illness his own pre-illness personality. It has been our experience that the patient's adjustment to his illness parallels his adjustment to his home situation and this, in turn, parallels his adjustment to the community and to employment. It is generally accepted that severe illness causes emotional regression. It is also known that the patient must be given the opportunity to adjust at his own pace toward his new self and the reconstruction of his body image. The problem is how to help the patient adjust to the extent that he can attain sufficient motivation to progress to his maximum capacity. Our experience has indicated that the hospital and aftercare program play a significant and important part in the joining of patient and family in the achievement of maximum rehabilitation for the patient so that, in the majority of situations, he can be returned to his community as a functioning citizen.

To help the patient and his family regain their stability and security, continuous positive supportive relationships are necessary. These must be realized by the patient from all members of the treatment team. Since there are so many disciplines involved in the treatment of the patient, free and continuous communication must always occur so that the treatment is consistent and neither the patient nor his family becomes confused. It is, therefore, very important that each member of the treatment team is aware of the goals set for the patient and how his discipline contributes to those goals. It is equally important that each member understands how his discipline relates to the other disciplines towards the patient's maximum rehabilitation. In general the program is carried out in two parts; the hospital program and the aftercare program.

On admission, a social and medical history is taken. The initial observations are compared with what is known of the patient's pre-illness situation as learned from the histories and an assessment is made of what changes will be needed to achieve his maximum capacity. As he begins to identify with and adjust to the illness realistically, daily activities are added to his general program. These vary with the individual but generally they include those that are seen as important in our culture and way of life and as a beginning transition to the community. Whereas initially the hospital and its facilities are used in the sense of a small community, gradually this part of the program is expanded into activities outside of the hospital. Among these activities in the order from the simple to the complex are included, excursions to the barber and beauty shops, restaurants, movies, theaters and museums. Initially this is done by the hospital staff. As the patient gains security and becomes sufficiently relaxed with each activity, the family, which is always kept informed of the patient's progress, is helped to take over this responsibility, initially under supervision of the staff and then gradually on their own.

Once the patient and family are comfortable with these activities, planning for weekends out of the hospital begins. This provides actual testing of the family's ability to function independently in their realistic environment outside of the hospital. Now strong emphasis and focus begins on the patient's adjustment to his community. This includes all of the roles and responsibilities society assigns to an individual and in this vocational planning is incorporated.

The timing of vocational planning and the extent to which it can be carried out is important and varies with each patient. Our experience has indicated that it must be well under way before the patient is discharged. Methods used in vocational rehabilitation vary in accordance with the individual needs. The least complicated planning involves those patients who can return to work with their former employer. In such situations, working with the employer towards a better understanding of the patient's illness, potentials and needs is started quite early. It is not uncommon for the patient to do actual work for his employer while he is still in the hospital. This is a most helpful device and lends itself admirably towards developing the patient's return to reality and the regaining of his security as well as for the establishment of a sound working relationship and mutual understanding between employer and employee. It is important that this be done in the hospital where support and counseling is available to the patient. In those cases where this is not possible one must plan in terms of retraining. This involves appropriate use and collaboration with other community resources. Many of these agencies have not had sufficient orientation, training or experience to deal productively with patients so severely involved. For effective planning with this group of patients, not only are positive relationships and a good understanding of the patient and his background necessary, but a great deal of ingenuity and imagination as well. Together with this there must be the ability to interpret the patient's needs to the community. The responsibility for this aspect of the work falls chiefly to the center social worker, as it is this discipline which acts as liaison between the patient and his community. The worker not only knows the patient and his family, but also is in the position to appropriately collaborate with the medical director and the other disciplines of the treatment team. From the beginning, the patient and his family become participants in all planning including plans for vocational rehabilitation, and when mutual agreement upon a concrete goal is reached, action is taken. In the specific area of vocational planning there are times when such goals can be developed with the patient and family only. However, in the majority of situations other community resources must become involved. Chiefly this work has been done cooperatively with the Department of Vocational Rehabilitation in the patient's community.

Since financial independence is given so much emphasis in our society and has so many meanings even for the nonhandicapped patient, it is understandable that the implications for the severely handicapped individual must be much greater. For these reasons, although initial discussion relative to vocational aspects varies with the individual, vocational rehabilitation is the last phase of the program to be completed. The patient must have regained security in all areas of daily living before he can successfully assimilate this final and most difficult step. By the time this has been achieved, the patient has usually had maximum benefit from hospital care and is ready for discharge.

By the time the patient is ready for discharge he has already had many experiences with his daily living activities in association with the hospital staff as well as with his family and friends through the weekend program. Nevertheless



facing the reality of severance from the specialized and sheltered environment of the center still creates some anxiety for both the patient and his family. Recognizing this, the patient and his family are given maximum support. They are given assurance of the continued interest of the staff and know that should any problems arise, assistance is readily available. However, it is emphasized that the function of staff is to provide help but not to take over responsibilities which rightfully belong to the family of which the patient is a natural and integral part. Although each patient must choose a personal physician for his routine aftercare, the patient remains in the medical program and is admitted for periodic evaluation. When an emergency arises the medical director is available to his physician for consultation and the patient may be admitted on his doctor's recommendation.

The aftercare program serves many purposes. The continuity of meeting medical and social needs for the patient by the professional disciplines who best know these needs offers security for the patient and his family. At the same time it has positive aspects for the center as well. Many of the projects started while the patient is still in the center are not completed at the time of discharge. This is particularly true of vocational goals. Our experience has shown that without continued participation of the center team which is familiar with the patient and his family, the goals set for the patient become diffused and there is regression.

No matter how well the hospital program is geared to meet the patient's home needs, there are vast differences between the hospital environment and that of the home and community. Frequently a home visit by the social worker, at times jointly with the occupational therapist if circumstances suggest it, needs to be made to help with home and community adjustment, and to facilitate daily living needs.

The frequency of the patient's return to the center for evaluation depends upon his physical condition, but during these readmissions a complete medical and social assessment is carried out and a plan for continued treatment is made. Social Service help is never terminated before the patient has reached his maximum rehabilitation. It is not uncommon that medical care may be continued beyond the point of the patient's social and vocational rehabilitation. In such instances the social service becomes active again as the need arises.

Although this communication places emphasis on those patients who achieved vocational rehabilitation, the report would be incomplete and distorted if it were not pointed out that the patients who went home but who were not considered to be vocationally rehabilitated also benefited from the center program beyond the strictly medical aspects. Since the therapeutic regimen is aimed at physical regain, mobilization and utilization of function, the patients are not permitted to spend protracted periods in bed and are not allowed to develop an attitude of invalidism. Those patients who do not attain significant vocational rehabilitation have gone through the same vigorous program of inside and outside hospital activities as the others and, similarly, the families have been oriented and instructed. Consequently, when they are discharged, these activities are con-

tinued at home. The significant daily periods out of bed permit movement throughout the home and the community. The prevention of invalidism and the attainment of mobility permit socialization and intellectual activities which represent social rehabilitation even in the absence of vocational attainment. As a consequence, the patient has status as an active, vital, important and, in some instances, even dynamic member of the family.

#### ILLUSTRATIVE CASES

For purposes of illustration two case histories are presented below. The first demonstrates the need for a clear understanding of the factors operative in the personality aspects of the patients and the necessity for working out vocational plans with those factors in mind. Further, the case shows the gains that can be made by continuing close relationship with the patient after discharge from the hospital.

The second case is of a young man who has attained no vocational rehabilitation as yet but who was rehabilitated socially nevertheless.

Case #1. T.K. is a white male who became ill with poliomyelitis on 11/11/54 at the age of 23 years. He was admitted to a hospital in his local Western New Jersey community where he rapidly developed respiratory paralysis and inability to swallow. A tracheotomy was performed and he was placed in a tank-type respirator. Complete paralysis of the neck and upper extremities soon followed. Because of the inability to swallow, he was fed through a nasogastric tube. His condition remained static following the acute phase of the disease.

At the time of his transfer to the respirator center at The Mount Sinai Hospital on 8/1/55 he was full-time in the iron lung, could not swallow and required feedings through a nasogastric tube. He had functional lower extremities and moderately strong abdominal muscles but was otherwise totally paralyzed in the trunk, neck and upper extremities. In addition, he had speech difficulties due to palatal and vocal cord paralysis (which prevented closing off or removing the tracheotomy tube) and his vital capacity was only 320 cc.

Ten days after admission he was permanently removed from the tank respirator through the substitution of a cuirass respirator. Thereafter he was up in a wheelchair, wore street clothes and could move himself around the center by propelling the chair with his lower extremities. After five months in the center his vital capacity was 650 cc (where it has remained), he could sit in his wheelchair all day and could breathe 4 to 7 hours without assistance while sitting up. The vocal cord paralysis persisted which required the continued use of the open tracheotomy tube. The swallowing difficulty improved after six months in the center so that feedings could be taken by mouth. The patient learned mouthstick activities, walked with assistance and learned to do several functions with his feet.

While the patient was in the hospital his wife and child lived with her mother so that Mrs. K. could work and maintain the family. His wife visited the patient regularly and demonstrated much concern and interest for his welfare. She did not complain and was found to be very realistic as to their situation. Throughout the patient's hospital stay he was controlling and unrealistic as to his home situation. Much of his attitude we learned from our observation of the patient, from the staff and from discussion with his wife. Although many attempts were made to help the patient talk about his feelings, he found it difficult to verbalize. It was when discharge planning began that many of his problems were uncovered. At this time he stated that he did not want his wife to work, maintaining that her place was at home with their child. At the same time he was unable to see his own limitations relative to employment and why his wife must work until some employment plan was worked out for him. For this reason he had the need to minimize every effort his wife made to help him. He refused to live in her mother's home even on a temporary basis, until the ground floor of their

own house was reconstructed to meet his present needs. While helping him to deal with these problems it became clear that the reason for the rigidity of his approach to them was because of their psychological implications. It was important for him to maintain his male role. For him this meant that he had to live in his own home where he could best control the situation. To retain this status, he had to be the head of the household and the wage earner. Whereas this created problems in their marriage, it had its positive aspects as well, as it motivated him to begin to explore vocational potentials much more quickly than most patients with such severe involvement. Once we were aware of the reasons for his anxiety, and could convey them to his wife, she was more accepting of them and better able to help him meet these needs. With this recognition he was permitted to move at his own pace in relation to vocational goals. He became very determined to start an insurance business which he could manage from his home. This was felt to be unrealistic for this patient in view of his severe physical involvement as well as the fact that it in no way related to his pre-illness vocational background. However, as the patient refused to consider other objectives the vocational counselor was consulted and confirmed our thinking. It was therefore agreed that the patient explore the insurance business further on his return home and that we would stand by to help him.

On 6/14/56 the patient was discharged to his own home with a trained attendant to help meet his physical needs during the hours that his wife worked. He learned for himself that an insurance agency from home was not feasible for him. He was ready then to accept referral to the Department of Vocational Rehabilitation. In consultation with this agency and the patient, it was possible to establish at his home an outlet business for the sale of sanitation equipment for homes and institutions. In addition to his own contacts and sales he had two salesmen on the road to whom he paid a commission. Shortly afterwards his income was sufficient to permit his wife to remain at home and to dispense with the services of the attendant.

On a home visit we found the patient pleased with his accomplishment. Also he learned, during this period at home, of his wife's sincerity and concern for his well being.

Whereas the patient was pleased with what he had accomplished he was not wholly content. The income was not enough to provide him with complete security and independence. It was suggested that he explore the feasibility of selling additional items to supplement his income. During his most recent admission for evaluation it was learned that the patient with several other handicapped individuals of varied vocational backgrounds, with approval of their community, started a new project for the handicapped. It is to include not only a sheltered workshop, but employment opportunities for the handicapped patient who is homebound as well. They have leased a building, secured several contracts from industry, and obtained a bank loan for operation. The patient is extremely happy not only because of his achievement and what this may mean to him in terms of income, but also because he is able to help other handicapped patients.

Case #2. R.L., a 26 year old male, became ill with poliomyelitis in 1949 at the age of 15 years. He was first admitted to a hospital near his upstate New York community where he rapidly became quadriplegic and required the use of a tank-type respirator. In 1950 he was transferred to another hospital in the vicinity of his home. A year after the onset of his illness there had been no return of muscle function and he continued to sleep in the tank respirator. He was free of respiratory assistance during the day by virtue of some respiratory muscle function and the use of self-taught glossopharyngeal breathing. For almost nine years the patient had not worn street clothes, spent almost all of the time in a private or semi-private hospital room, had not used a wheelchair and had left the hospital only for occasional brief excursions. Although his home was only ten minutes away from the hospital, on the rare occasions when he visited there, he had to return to the hospital to sleep in the iron lung.

In 1958 he was transferred to the Respirator Center at The Mount Sinai Hospital. During his stay in the center the patient's muscle paralysis did not change nor did his vital capacity

of 550 cc increase. Nevertheless a cuirass respirator and rocking bed were used for artificial respiration so that the tank respirator was no longer needed. A wheelchair was provided and the patient soon could tolerate sitting up almost all day. Mouthstick activities were taught and with them he could turn pages, type with an electric typewriter, and paint.

He was transferred to the Respirator Center at The Mount Sinai Hospital without prior adequate interpretation for the move having been given him or his family. They were anxious and hostile and did not understand why the transfer was made. The parents felt that the control of their son was no longer theirs but in the hands of some vague bureaucracy. Psychologically both the patient and his parents had become resigned to permanent hospitalization and were very much upset to have this situation disturbed.

Although on admission the patient was over 24 years old, he seemed to have remained an adolescent emotionally. Initially he acted out his anxiety and insecurity by continuously letting his presence be known. The program and purposes of the center were explained to the parents but only after several conferences were they able to understand that the patient was still their son and their responsibility. They were helped to understand that ultimately all decisions regarding his future even to the extent of going home or to another hospital were his and theirs.

Clarification of the reasons for transfer also had to be made to the patient. Whereas the program and its aims were explained to him there seemed to be little interest on his part. It was during discussions as to why he demonstrated so little interest in returning to his home that many of his feelings were uncovered. He stated that if his parents wanted him home, they would have taken him three years ago. It became apparent that although outwardly resigned to permanent hospitalization he was angry with everyone including his parents. We helped him to examine some of the realities in the situation. Gradually with a positive consistent relationship, he began to understand that what he believed to be his parents' disinterest was in reality their concern. They did not know how he could be managed with safety at home, nor did they know of the various services available to them to help with his care. He began to recognize that they really had no way of knowing this without being informed by those professions oriented and experienced in dealing with his problems.

We recognized with the family how difficult all this must have been for them and conveyed to them our concern and interest. As a positive relationship was established they were better able to talk about their anxieties. In addition to the concern for the patient, there were financial problems. We assisted them with transportation costs so they could visit the patient regularly. We gave them assurance that if the father did not have regular employment soon we would help them with referral to an appropriate agency for financial assistance. We also explained the kind of attendant care available to the patient.

Gradually the patient became more alert and began to relate to the medical program. He talked to the other patients about their weekends at home and was excited over their reports. With this stimulation and added security he began to move into activities out of the ward and then out of the hospital. His most exciting experience was traveling to Philadelphia to see the Dodgers play. He learned for himself the advantages in mobility between a wheelchair and a stretcher. By this time the patient was also no longer using the tank respirator. He realized that with this freedom he could visit with relatives for weekends in the country which was not possible before. He could turn pages and use the electric typewriter by mouthstick.

As he began to see greater potentials for his future, a new personality began to evolve. Both staff and patients enjoyed his keen sense of humor, but those disciplines who worked with him more closely recognized a maturing quality. With this came a more positive relationship with his parents as well, for which they were very grateful. When they saw the patient's progress and changes in personality, they began to look for more functional housing. This added to the patient's convictions and security that his parents wanted him home. About the same time the father found regular employment. With this added security both the patient and family began to ask for an approximate date for discharge. The patient agreed that it would be helpful to have a trial weekend at home and that it would offer him



and his parents greater security for the final step. In planning for the weekend, we discussed with the family the importance of noting any problems so that they might be dealt with prior to discharge. The patient enjoyed his experience. There were no major problems. From their observation it was apparent that to help care for the patient at home, an attendant would be needed for eight hours daily, five days each week. The patient participated in all of the planning. It was he who composed the newspaper advertisement for the attendant in his community paper. His needs were stated with clarity and practicality. He openly expressed appreciation for his independence and new responsibilities. The patient was discharged to the care of his family and has continued to be active at home. He is up and about in the home and in the community and has expressed his happiness about being reunited with his parents.

His background, lack of training, lack of work experience and degree of paralysis make vocational attainment very unlikely although some possibilities are being explored. However, even though no vocational attempts are fruitful, this patient has been rehabilitated in a social sense, for he is functioning at a high level socially and is not a chronic invalid living out his days in the confines of an institution for chronic diseases.

#### SUMMARY

In this communication we have attempted to delineate the methods which we have found to be effective in supplementing and complementing the strictly medical care of patients stricken with catastrophic illnesses. Whereas the patients referred to in this report have severe and extensive residua of poliomyelitis, including respiratory inadequacy, our experience indicates that the methods used do not apply only to that group. Many patients suffering from the effects of other severely disabling illnesses and in need of long periods of hospitalization for physical and personal restoration have similar problems which are amenable to the approach presented here.

The widespread physical deficiencies result not only in functional loss but in depersonalization, regression, family upheaval and economic catastrophe. Excellent medical and physical therapy can result in remarkable functional regain even if only by virtue of prosthetic and adaptive devices. Yet these are inadequate for the provision of acceptable end results unless a well planned, consistent, coordinated ongoing program is carried out with the active participation of informed vigorous paramedical members of the treatment team. This is imperative since no one person or single discipline is able or equipped to meet the many diverse needs of these patients. This report has presented the techniques used during and after hospitalization which in our experience have resulted in the restoration of function, productivity, personality and dignity.

# SURGICAL TREATMENT OF PULMONARY METASTASES

## REPORT OF A SUCCESSFUL CASE WITH FIVE YEAR OBSERVATION

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The appearance of a pulmonary metastasis in a patient who has undergone surgery for malignant disease elsewhere in the body need not invariably occasion a hopeless prognosis.

The following case report illustrates the successful removal of such a lesion seven years after abdomino-perineal resection for rectal carcinoma, with survival and apparent freedom from disease five years after lobectomy for a cluster of metastases.

### CASE REPORT

G. A., Mount Sinai Hospital #52523 (First admission 11/19/48–12 17/48). This forty-six year old white female was admitted with a six-week history of rectal bleeding due to a rectal carcinoma. She had had an episode of pneumonia in 1942, but was otherwise well. Physical examination revealed a polypoid mass palpable on the posterior rectal wall about four inches from the anus. An abdomino-perineal resection (Dr. John H. Garlock) was performed 11/24/48. Pathology report #P42371. *Gross description:* The specimen consisted of a forty-five cm length of colon, rectum and anus. Beginning eleven cm above the mucocutaneous junction on the mesenteric border there was a five cm irregular somewhat flat, but polypoid tumor without ulceration, with a definitely infiltrating firm edge. Its consistency varied from soft to hard. *Microscopic diagnosis:* "Polypoid adenocarcinoma of colon with early infiltration. No involved lymph nodes found." (Fig. 1).

The patient was asymptomatic for the next seven years. She was seen at frequent intervals during this time. However, readmission to the hospital was required in 1955. (Second admission 9/4/55–9 24/55). She now gave a two month history of mild cough productive of a small amount of whitish sputum flecked with streaks and clots of blood. There were no wheezes, nor dyspnea or weight loss. She had an occasional twinge of left upper anterior chest pain above the left breast. Mild arthralgias were present. Appetite was good. On physical examination she appeared well. There was no lymphadenopathy and the thyroid was normal. The breasts were free of masses. A few fine rales were detected over the right lower lobe laterally. There was no bony tenderness, clubbing or pulmonary osteoarthropathy. The abdomen presented a well-functioning colostomy. There were no abdominal, perineal or pelvic masses or any other evidence of recurrence of the original rectal tumor.

X-ray of the chest showed a fusiform shadow in the anterior basal segment of the right lower lobe (Fig. 2). Tomography revealed a fairly well-circum-

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scribed nodular density in this area with distal atelectasis and with linear strands extending toward the hilum (Fig. 3). No other infiltrations were noted. There was no pleural effusion. Bronchoscopy (Dr. Max Som) failed to demonstrate any endobronchial tumor, but secretions obtained from the right lower

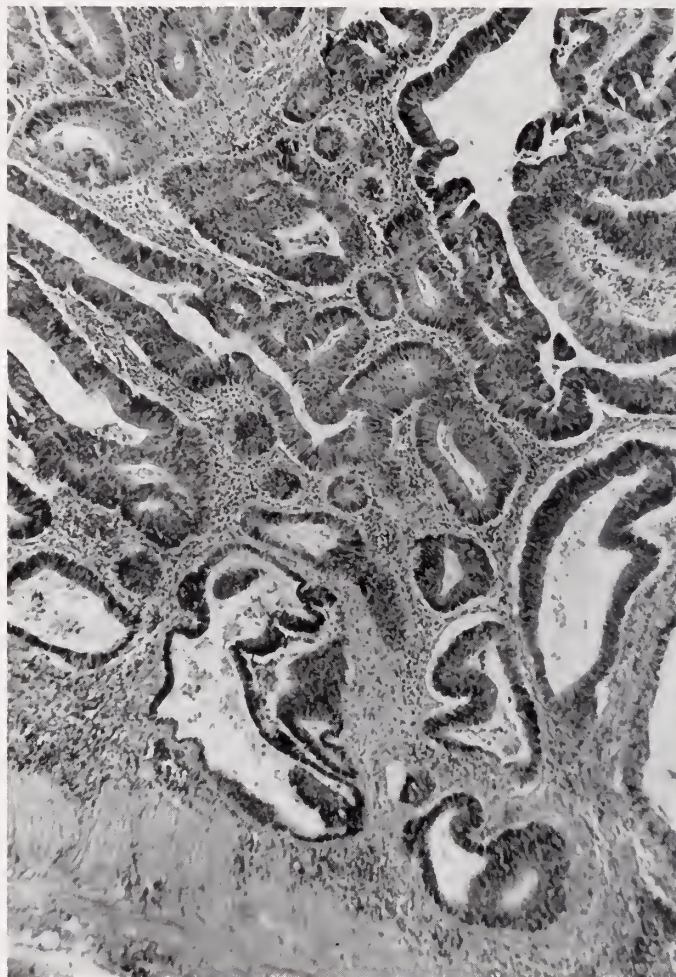


FIG. 1. Photomicrograph of Primary Rectal Carcinoma.

lobe bronchus showed tumor cells. A clinical diagnosis of primary peripheral pulmonary carcinoma was made.

The patient was operated on on 9/9/55 (Dr. Paul A. Kirschner). The anterior basal segment of the right lower lobe was infiltrated with whitish tumor tissue. There were no enlarged hilar nodes or pleural fluid or implants. Since the involved area was adjoining and in contact with the middle lobe (although not adherent) a bilobectomy of the lower and middle lobes was performed. Pathol-

ogy report #P74285. *Gross description:* (Fig. 4) There was a tumor in the anterior diaphragmatic edge of the right lower lobe measuring six cm in its greatest diameter. It was nodular in outline and numerous nodules projected from the pleural surface. Slight umbilication was present in one large nodular area on the diaphragmatic surface. On gross section the tumor was found to be yellowish and necrotic, and it revealed very little anthracotic pigmentation.



Fig. 2. Conventional x-ray of Chest. September, 1955.

Note the metastatic lesion in the right lower lobe.

Around the periphery of the large tumor were numerous smaller nodules which were separate from the main tumor. These nodules also had a central necrotic portion and a peripheral nodular yellowish slightly gelatinous zone. Bronchi and veins were invaded in the area of the tumor. *Microscopic diagnosis:* "Multiple adenocarcinomata of lung, (one large and two small), probably metastatic. No involved lymph nodes found." (Fig. 5)

The patient has been followed carefully by means of repeated physical examinations and roentgenograms of the chest through May, 1961. No further evidence of malignant disease has appeared. She has been asymptomatic. (Fig. 6)



## DISCUSSION

The prerequisite for success in the surgical treatment of malignant disease is the localization of the tumor to an area that can be circumscribed and resected in one piece. This degree of localization varies from a very small site, as occurs in a minute skin carcinoma, to widespread involvement of a major viscus and its regional lymphatic drainage. The latter can be excised en bloc,

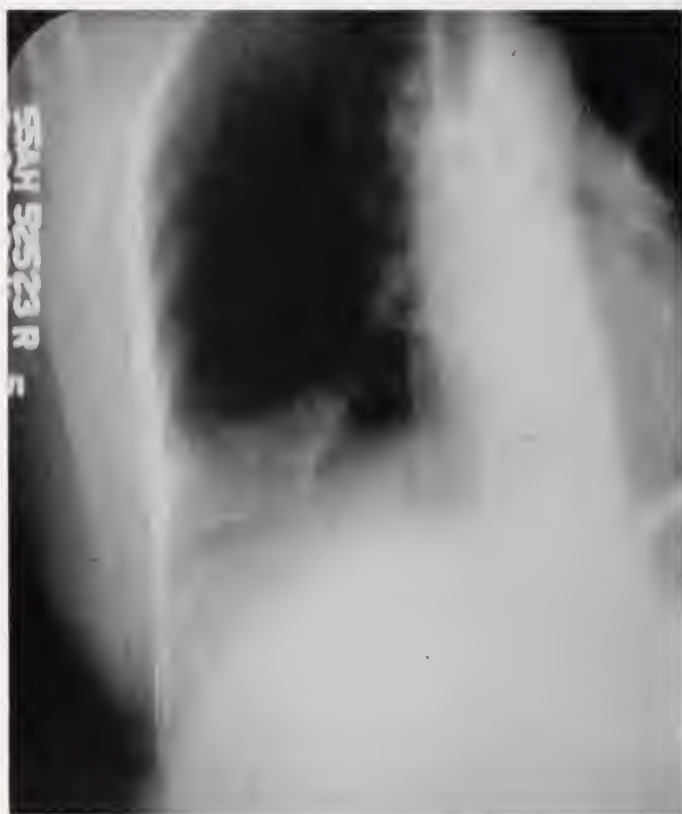


FIG. 3. Tomogram of Right Lower Lobe. September, 1955.  
Note Nodular Configuration of Lesion.

albeit with much more difficulty and with graver implications as regards morbidity, mortality and physiological derangement. Unfortunately, too many patients even with locally favorable lesions have distant blood-borne metastases which preclude curative surgical procedures.

However, a situation may occur in which the only evident distant metastasis appears to be a solitary lung nodule or a localized cluster of such nodules. Detection of such lesions in the lung is relatively easy because of the accessibility of this organ to roentgen examination. Similar lesions in a solid viscus such as the liver will always go unnoticed until increase in growth discloses their presence by palpation.

The appearance of one hematogenous metastasis is usually a sign of more widespread dissemination. But, occasionally, in fortuitous circumstances, the evident metastasis may be the only one. In such an instance, as in the case reported here, aggressive surgical treatment of the secondary lesion may yield a cure.

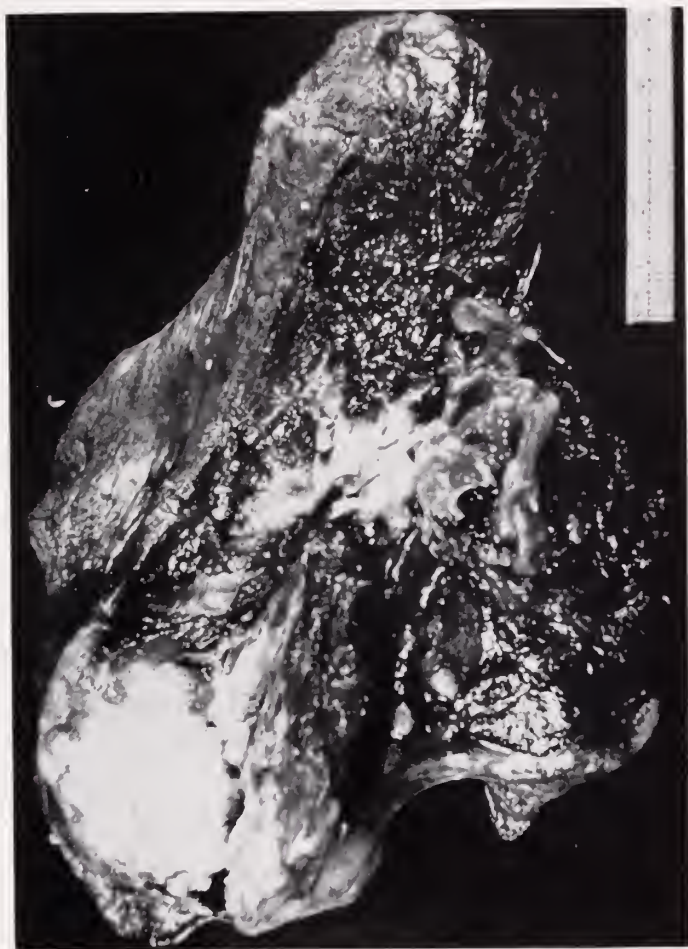


FIG. 4. Photograph of Resected Specimen Showing Nodular Lesion in Right Lower Lobe.

Malignant cells have been found in the circulating blood in a high percentage of patients undergoing resectional surgery for malignant disease (1). Such cells exhibit tremendous variation both in viability and in capacity to take root and grow in distant organs like the lung. This has been confirmed experimentally. Indeed, such cells have been identified in the blood stream of patients who have subsequently fulfilled the rigid criteria of the surgical cure of cancer (1).

The rate of growth of seeded viable cells into evident tumor masses is also subject to great variation, a biologic characteristic also true of primary neoplasms. In addition, viable cells may be dormant for years, only to suddenly

manifest themselves as gross metastatic lesions long after the original growth is deemed to have been cured. The reason for this sudden burst of vitality is unknown. The case herein reported may well be an example of this.

Rather than leave the future to chance, attempts are being made to destroy

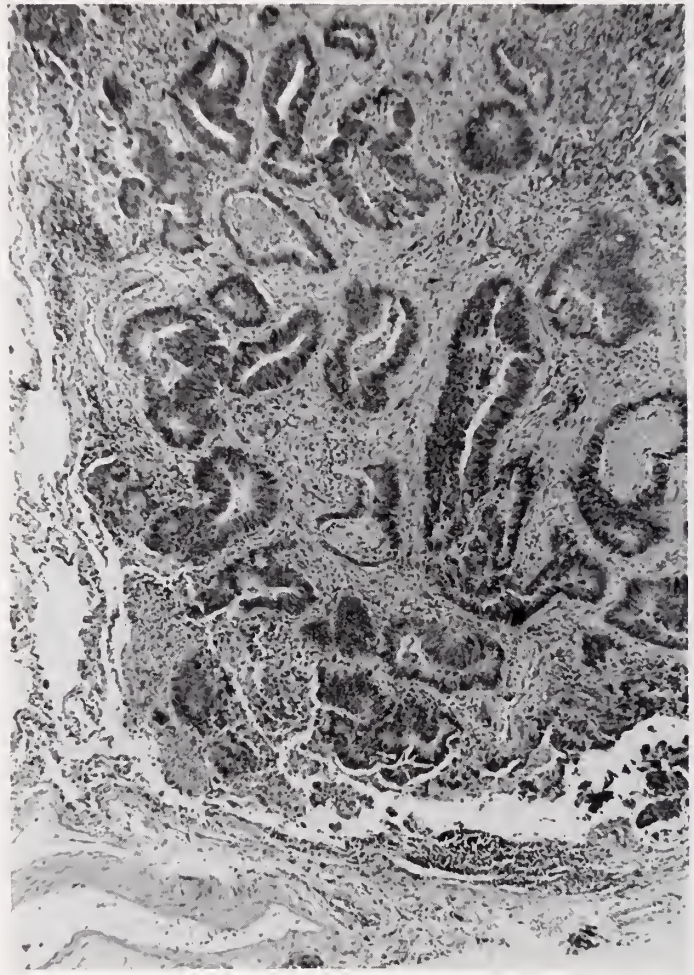


FIG. 5. Photomicrograph of Metastatic Lung Tumor.  
Note Glandular Structure Identical with that of Primary Tumor.

viable cancer cells which may have been spread beyond the field of surgical attack by the systemic administration of cancerocidal substances at the time of local and regional surgery (2, 3).

Deliberate surgical therapy for metastatic lung lesions has paralleled the growth and development of thoracic surgery. The trepidation of Divis in 1927 (4) and Torek in 1930 (5) gave way to increasing confidence of Barney and Churchill (6), and Alexander and Haight (7). At this time, based upon several

hundreds of cases (8 to 17) a clinical pattern has emerged which permits a reasonably optimistic approach in selected instances, although as Alexander has said, in any individual case both the patient and the surgeon are gamblers.

Certain types of primary tumors are more prone to produce resectable metastases than others. Epithelial neoplasms of the kidney and colon, and sarcomas of connective tissue appear to make up the bulk of the metastatic lesions that have been successfully treated (8 to 17).



FIG. 6. Conventional x-ray of Chest Five Years after Bilobectomy.  
The lung fields are clear.

The time interval between the removal of the primary tumor and the appearance of the metastasis may be of some significance. Ordinarily the longer the interval the more favorable the circumstance. This is an expression of the workings of natural selection, for large numbers of unfavorable cases fall by the wayside in the early postoperative months and years. However, occasions arise in which the metastatic lesion may be recognized and even removed prior to resection of the primary tumor with successful long-term outcome (6).

In melanoma, long latent periods between the primary lesion and the appearance of metastases are common but the basic high malignant potential of this tumor is well-known and successful treatment of metastases is rare.

The question of symptomatic benefit of resecting a solitary pulmonary me-



tastasis should be stressed. Most commonly such lesions are asymptomatic and are discovered by the more liberal employment of routine chest x-rays. However, in our case hemoptysis was the presenting symptom. It is now known that metastatic lung tumors may involve large bronchi and as such may act in a manner indistinguishable from primary neoplasms by producing hemoptysis, bronchial obstruction and pneumonitis (18, 19). Nevertheless, the same sophistication of aggressive attack upon asymptomatic primary tumors should be applied to appropriately selected metastatic lesions.

A final important clinical point is the good possibility that the lung tumor may actually be an independent primary growth, and deserving of therapy in its own right (20). It is a substantiated fact that a patient who has already had one malignancy becomes many times more susceptible to the development of subsequent independent tumors than he was to the first one. Therapeutic orientation should be aggressive here also.

The indications for surgery for pulmonary metastases may be listed as follows:

1. The primary lesion should have been completely eradicated and there should be no local recurrence.
2. The longer the time interval between the removal of the primary and the appearance of the metastasis the better. However, a successful outcome can occur even if the metastasis is removed before the primary tumor is discovered and treated.
3. The metastatic lesion should best be solitary. If not, it should be localized to areas of the lung which can be encompassed by a reasonable degree of lung resection without excessive sacrifice of functioning parenchyma. For example, it may be located in two contralateral lobes, be clustered in one lobe (as in this case) or confined to one lung.
4. The patient should be able to meet the physiological demands of lung resection, including pneumonectomy, as determined by tests of his pulmonary and cardiovascular function.

In brief, the same criteria for the surgical treatment of a primary lung cancer should apply to the treatment of a solitary or localized metastasis.

#### SUMMARY

1. A case of carcinoma of the rectum with a localized cluster of pulmonary metastases in which successful surgical treatment of both lesions was achieved has been presented. This patient developed the metastases seven years after the removal of the primary and is alive and well five years after a bilobectomy of the right lower and middle lobes.

2. There is ample pathological and clinical evidence that solitary or localized metastatic lesions occur in the lung.

3. The lung is a fruitful organ for the discovery of such lesions because of its accessibility to frequent and repeated detailed roentgen examinations.

4. The clinical criteria for the removal of pulmonary metastases are essentially the same as those for the excision of primary tumors. Emphasis is placed

on the conservation of lung tissue, although occasionally pneumonectomy may become necessary.

5. Resection of such metastatic tumors may be followed by prolonged survival and cure.

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# *Clinico-Pathological Conference*

## PROGRESSIVE CARDIAC FAILURE WITHOUT PAIN OR MURMURS IN A 62 YEAR OLD MAN

*Edited by*

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A 62 year old Negro mailman was admitted to The Mount Sinai Hospital for the second time complaining of shortness of breath for two months.

*1st admission* (9 months earlier). The patient had been well until six weeks prior to admission when he noticed a choking sensation in his throat and breathlessness when walking uphill along his mail route in the cold weather. This was relieved by rest but would recur on exertion. At the end of the day his ankles were swollen but they were normal by morning. No pain was experienced. He was seen by his physician who gave him digitalis, two injections of mercurial diuretics, and placed him on a low salt diet. He had a good diuresis and his symptoms subsided. He stopped working and was able to get around at home until the last two weeks before admission when the shortness of breath returned and progressively increased. The ankle edema had not recurred and the patient had no pain nor orthopnea.

The patient stated he had been in good health all his life and that he had been treated for gonorrhea 40 years earlier. His mother died of a stroke at 56 years of age and his father died at 85 of unknown causes. He was one of 11 siblings, the rest of whom were living and well. He worked for the Post Office for 30 years, smoked a pipe for 35 years, did not use alcohol and took only the medicine recently prescribed.

The temperature was 99.4° rectally, pulse 104 min., respirations 22 min. and blood pressure 170/100 in the right arm and 160/95 in the left arm. He was flat in bed in no acute distress. The ocular fundi showed moderate vascular tortuosity with minimal narrowing and no papilledema. The teeth were in poor repair. The posterior pharynx was injected. A left supraclavicular node was palpated. The cervical veins were distended even in the upright position and a hepatojugular reflux was demonstrated. The trachea was in the midline. Fine crepitant rales were heard in both lung bases and left axillary nodes were felt. The heart was enlarged to the left with the PMI in the sixth interspace at the anterior axillary line. Sinus rhythm was noted with a protodiastolic gallop heard over the entire precordium and loudest along the left sternal border at the third interspace. No murmurs were heard. The abdomen was protuberant and a sharp, nontender liver edge was felt five fingerbreadths below the costal margin. A

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draining perirectal abscess was present. Slight pitting sacral and ankle edema and some clubbing of the nails were seen. No cyanosis was noted. No neurological abnormalities were elicited.

Urinalysis showed 4+ albuminuria which later disappeared with no sugar or formed elements. Specific gravity varied from 1.001 to 1.018. Hemoglobin was 15.2 Gm%, wbc 9,000/mm<sup>3</sup> with 65% segmented cells, 24% lymphocytes, 4% monocytes, 7% atypical lymphocytes. Toxic granules were present in the leukocytes. The sedimentation rate was 23 mm/hr., BUN 13 mg%, creatinine 1.6 mg%, blood glucose 92 mg%, CO<sub>2</sub> 30.2 mEq/l., sodium 146 mEq/l., potassium 4.7 mEq/l., chlorides 107 mEq/l., uric acid 6.2 mg%, serum albumin 4.0 Gm%, serum globulin 3.4 Gm%, serum cholesterol 220 mg% with 165 mg% esterified, serum bilirubin 0.4 mg%, cephalin flocculation negative. Tuberculin test was positive with PPD  $\times$ 1. A Frei test was equivocal. Blood cultures were negative. Cultures from the perirectal fistula grew *A. aerogenes* and a nonhemolytic, coagulase and mannite negative staphylococcus albus. Various complement fixation and agglutination tests were negative. Venous pressure was 240 mm of water and the circulation time (Deeholin) was 45 seconds.

Chest x-rays showed the heart to be moderately enlarged to the right and left. The pulmonary artery segment was not prominent. The aorta was elongated and some calcification was seen in its arch. The lung fields were clear and there was blunting of the right costophrenic sinus. A retrocardiac impression was seen on the barium filled esophagus at the level of the left atrium. The electrocardiogram showed a rate of 100, PR interval of 0.15 sec. and QT duration of 0.3 sec. The ST segment was depressed and T waves were inverted in leads I, aVL and V5 and V6. An embryonic Q with a small r deep S pattern was present in leads III and aVL and a wide prominent S1 was seen. The vectorcardiogram suggested an anterior wall infarct but there was also delay in the initial part of the loop, compatible with incomplete LBBB.

He remained in the hospital six weeks during which time he lost 13 pounds and all signs of congestive failure disappeared although the heart remained strikingly enlarged. Several blood pressure readings were normal and the venous pressure had been reduced to 85 mm and circulation time to 28 sec. The perirectal fistula healed and the patient was sent home.

*2nd admission.* The patient remained well for four months after discharge when edema and dyspnea returned despite continued therapy. Pain was never present.

On examination he was afebrile, his pulse was 106 and regular, and his blood pressure 118/70. Large symmetrical bumps were seen on the hard palate. Breath sounds were decreased at the right lung base and a few crackling rales were heard in both bases. The heart was enlarged as before and the same split second sound was heard. The liver was down five fingerbreadths and ascites and severe edema of the legs, thighs and sacral area were present. A draining abscess was present on the right buttock.

Venous pressure was 265 mm and rose to over 600 mm with hepatic pressure.



Circulation time was 45 sec. Chest film showed bilateral pleural effusions more marked on the right. Fluoroscopically, the pulsations of the large left ventricle were small, the aortic window was not clear, the right ventricle did not fill the retrosternal space and the barium filled esophagus bulged posteriorly. Urinalysis showed 2+ albumin and a few white cells with normal specific gravity. Later the albumin increased and red cells and hyaline casts were seen. Hemoglobin was 16.5 Gm%, WBC 8,700/mm<sup>3</sup> with a normal differential, and sedimentation rate 4 mm/hr. BUN was 34 mg%, blood glucose 62 mg%, CO<sub>2</sub> 22.4 mEq/l, chlorides 9.7 mEq/l, sodium 138 mEq/l, potassium 5.1 mEq/l, albumin 3.4 Gm%, globulin 3.3 Gm%, bilirubin 2.2 mg%, cholesterol 190 mg% with 145 mg% esters and glutamic oxalacetic-transaminase 45 units. The electrocardiogram showed low QRS and T wave voltages. A small q tall R was present in a VL and V1 while a small r deep S were seen in III and aVF. QRS was W-shaped in V4 and a QS complex was found in V2 and V3. The ST segment was depressed in V5 and V6.

Despite vigorous digitalis and diuretic therapy, the patient did not lose any fluid. He continued to be orthopneic and tachypneic and cyanosis was noted. A thoracentesis was performed on the right and 1,200 ml of cloudy serosanguinous fluid was removed which did not clot and had a specific gravity of 1.012. Most of the cells were erythrocytes. Despite the thoracenteses, the patient's distress continued and he expired on the 7th hospital day about 11 months after the onset of symptoms.

*Dr. Herrman Blumgart\**: As I see the problem in this case, this patient had congestive heart failure and also damage of the left ventricle, probably the anterior wall. The fascinating problem to me is what caused the congestive heart failure and the damage to the left ventricle. There are a few subsidiary problems of interest such as whether he had pulmonary embolus or not. The entire illness of our patient is one year in duration. I interpret the choking sensation in his throat when he walked, as dyspnea rather than angina pectoris. He had no prior difficulty although he was a postman. We know that he showed no chest pain previously or later when he had recovered from his decompensation. Of course he could have had an acute myocardial infarction and lost quite a bit of heart muscle but we had no such history. So we are really still quite in the dark, it seems to me, in regard to the etiology. In looking for queer causes of congestive failure, we might think of Chagas' disease; but he had never been out of the country. Knowing he had been in good nutrition, we cannot think of beriberi heart disease or nutritional difficulties of that sort. There is no history of syphilis.

There was no evidence on physical examination of aneurysm or Poulet's disease. The blood pressure was definitely elevated initially but all the later blood pressures, including the intervals between admissions, were always normal. Whether there was a pre-existing hypertension in this man that might have led to cardiac hypertrophy and congestive failure cannot be said. In view of the

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fact that the ocular fundi showed moderate vascular tortuosity with minimal narrowing, and no papilledema and all the other blood pressures were normal, I am inclined to feel that the initially high blood pressure was due to excitement or nervousness and that this man was not really suffering from hypertensive heart disease. A left supraclavicular node was palpated. This brings me to a problem which I will put to one side and not discard—whether this man had malignancy or not. I assume the node was not biopsied. No mention is made of it in the later admission, which is peculiar because if there were a node, I should think they would have found other nodes, certainly in his second admission, and this one would have received more attention. The protodiastolic gallop heard over the entire precordium is consistent with congestive heart failure. This is usually held to be failure attributable to the right ventricle and he certainly seemed to have both right and left ventricle failure. Did he have rheumatic heart disease? If he had rheumatic heart disease, one would certainly have expected a man of 62 to have had some murmurs, some congestive failure or dyspnea in the past and to have a gradual onset when he came in or to at least show some evidence of valvular disease. To come in without any history and rapid onset is unusual. We do know that mitral stenosis and a very tight mitral stenosis may occur without murmurs. To have this man go right into this stage of congestive failure without physical signs of valvular disease, with an acute history of one year from beginning to death seems to me to be very strongly against rheumatic heart disease. Since I have to deal with probabilities, I shall not make a diagnosis of rheumatic heart disease.

The laboratory tests fail to lead me to any diagnostic conclusion. He showed neither elevated blood sugar nor glycosuria speaking against hemochromatosis. The fact that the tuberculin test was positive tends to make unlikely another cause of congestive failure which is sometimes seen, though rarely, and that is sarcoidosis. I suppose we have to think of the rare causes of congestive failure in this man with draining sinuses. He may have had amyloid which thereby would have accounted for his large liver and also for damage to his left ventricle which could go on to congestive failure. The difficulty is, if you relate amyloid to his infection, it would be on the basis of secondary amyloidosis, in which it is very unusual to find enough damage to the heart to cause congestive heart failure. This form of amyloidosis does occur, particularly in older individuals in the 70's, but not usually at this age. I think amyloidosis may be a diagnosis that is going to trip me. A Congo Red test and a needle biopsy of the liver were apparently not done. The latter would have been the decisive test so far as amyloid was concerned. I am not going to make that diagnosis because of the age, the rapid course, and the fact that it was related to his infection.

We will see the x-rays next.

*Dr. Sigmund Brahms\**: The chest x-ray showed some enlargement of the heart, predominantly toward the left. There was some increase in the promi-

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nence of the convexity of the ventricular contour. The pulmonary vascular markings were perhaps a little prominent in the hilar region and the periphery is distinctly less prominent. There was no discrete infiltration. We did not see any evidence of fluid in the pleural space on either side. The initial x-ray showed only a large heart with no roentgen evidence of congestive failure at that time.

The later picture was quite different. We saw pleural effusion in both pleural



FIG. 1. Barium filled esophagus showing indentation caused by enlarged left atrium.

spaces. It was less extensive on the left side and quite extensive on the right. There was either a patch of infiltration in the lower half of the left lung or perhaps some fluid in the fissure. A heart shadow was largely obscured by the effusions. The lateral film showed a very peculiar localized impression on the barium outlined esophagus at the level of the left atrium (Fig. 1). This would suggest the presence of left atrial enlargement. In the frontal film, we saw no evidence of a double density within the heart shadow to suggest an enlargement of the left atrium and no localized prominence of the left border in the supraventricular region which would represent a dilated auricular appendage.

*Dr. Blumgart:* This is a fascinating x-ray because it shows a rather sharp indentation there at the level of the left atrium. We know that congestive failure may occur in some individuals on the basis of recurrent pulmonary embolization but there is no evidence of recurrent pulmonary embolization. Nor can we account for it on the basis of cor pulmonale. The enlargement of the left ventricle also rules out, to my mind, rare conditions which may cause impairment of the filling of the left ventricle such as myxoma of the atrium or ball valve thrombosis.

The electrocardiogram is abnormal but not diagnostic of an acute myocardial infarction. It indicates incomplete left bundle branch block. I am somewhat bothered because we know in amyloidosis of the heart we have deposition of amyloid in the muscle fibers and that we can have what has been aptly termed electrocardiographic infarction of the heart with heart muscle damage that is quite localized, and simulate what we usually see as acute myocardial infarction in some people with patent coronary arteriosclerosis. Still, though, I think we do not have that here. I think it simply means we have damage to the left ventricle.

After he lost 13 pounds and all signs of congestive failure disappeared, the heart remained strikingly enlarged. This is a very interesting thing to me because after a person has had congestive failure the heart tends to lose its dilatation and diminish considerably in size. The signs of congestive failure disappeared but the heart remained strikingly enlarged in a man who had a normal blood pressure.

I do not know what those large symmetrical bumps were on his hard palate unless they be what is called torus palatinus seen in 60 per cent of the Eskimos and rare in the Hottentots. But I am rather disturbed by this because they were not present at first. If they were, they were not noted. One wonders if they were sarcomas. They are on the hard palate and occur quite frequently. They never become malignant and never are of any concern to anyone unless it be the poor patient when he tries to get false teeth to fit the roof of his mouth.

To summarize, I believe it to be most improbable that the patient had arteriosclerotic heart disease, luetic heart disease, Chagas disease, thyrotoxic heart disease or hypertensive heart disease. I do not believe we have enough here to make a diagnosis of tumor with a secondary or primary involvement of the heart. I would have expected more in the way of arrhythmias. There is no rheumatic heart disease, no evidence of sarcoidosis, no evidence of the cyanotic group of diseases, no cor pulmonale, no myxoma, no ball valve thrombus, no constrictive pericarditis or myocarditis.

Therefore, we have a patient who had congestive failure and cardiac enlargement of unknown cause. This patient falls into a fascinating group that is called idiopathic cardiac hypertrophy. Even the terminology is subject to question. Most of these patients are seen at an early age but some have been reported as old as this man. This condition forms a rather motley group and it includes patients that are given different diagnoses by different groups of pathologists. It has been called myocarditis of unknown etiology. Elster, Horn



and Tuchman reported ten cases of this condition which they had seen in 15 years (1). Levey talked about this condition in the early literature and found some 14 cases that might be similar to this in 184,000 admissions (2). Five of these were found in 3,154 autopsies.

My diagnoses are congestive heart failure, primary idiopathic myocardial hypertrophy involving particularly the left ventricle with some fibrosis. Two possibilities which I must raise are mural thrombosis and pulmonary embolism.

*Dr. Samuel Proger\**: I wanted you to be sure Dr. Blumgart and I had not gotten together beforehand so I wrote out a few of my comments. They are not in agreement with those of Dr. Blumgart so that either one or both of us could be wrong.

We have a 62 year old man with two episodes of what appear to be heart failure, the second one intractable. The answer to the first question, namely, etiology, may provide the answer to the second, namely, the intractability.

As to etiology, the first and obvious possibility is coronary heart disease. He had a suggestive history of chest distress and there was mild hypertension. There was, however, no definite history of acute coronary heart disease and the hypertension was not impressive. Furthermore, the subsequent course, especially on the second admission, was not consistent with this etiology. Even on the first admission, it is of interest that despite increased venous pressure, edema and hepatomegaly, there was no orthopnea and the lung fields on x-ray were clear. That is to say, there was no evidence of left heart failure to match the right heart failure if the cause were coronary or hypertensive heart disease.

The glands appear to play a prominent part in the picture. There were the enlarged left axillary nodes and there was the palpable left supraclavicular node. Also the esophagus deformity was such as might have been produced by enlarged nodes in the tracheal bifurcation. In fact, if the indentation of the esophagus had resulted from an enlarged left auricle which is suggested here, the esophageal deformity might have been expected to extend for a greater distance downward than was the case. It was the result of a notched out area that was almost too sharply delineated for a left auricle.

The adenopathy might conceivably be related to the cardiac picture in various ways such as tuberculosis, sarcoidosis, lymphoma, amyloidosis, and carcinomatosis.

As to tuberculosis, there was the positive tuberculin test which of course need not be of significance at this time. Could the patient have had tuberculous pericarditis? The high pulse pressure on admission in spite of the high venous pressure from presumed interference with venous return, the absence of fever, pericardial pain or rub, and the remittent course would all suggest that we are not dealing with tuberculous pericarditis. However, the nodes, the evidence consistent with constrictive pericarditis, the perirectal abscess that might conceivably have been tuberculous with secondary infection, and the positive tuberculin test all make tuberculous pericarditis a diagnostic possibility.

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As to sarcoidosis, there is no evidence for this diagnosis except the adenopathy. There was certainly no evidence of pulmonary sarcoidosis that might result in right-sided failure from cor pulmonale, and even if there were granulomatous changes in the heart muscle, the failure would not be likely to be so overwhelming, certainly not as a more or less isolated finding. Also, there is the positive tuberculin test which is unusual in sarcoidosis.

As to lymphoma, the glandular distribution is unusual as is the absence of fever and splenomegaly. Lymphoma remains, however, a theoretical diagnostic possibility with pericardial involvement.

As to amyloidosis, the chronic infection and the positive tuberculin test raise this possibility. Hence, if the patient had amyloidosis, it was presumably secondary. While there is myocardial involvement in secondary amyloidosis, it is rarely sufficient to produce intractable failure. If this is heart failure due to primary amyloidosis, the absence of recognizable extracardiac manifestations of primary amyloidosis such as macroglossia and skin lesions would make this diagnosis impossible clinically. However, the cardiac picture alone is not inconsistent with amyloidosis.

We come next to carcinomatosis with cardiac involvement. In many respects, insofar as I can see, the picture fits this diagnosis most readily. There is the adenopathy, especially what appears to be mediastinal adenopathy. This type of adenopathy when due to carcinoma could be expected to develop most frequently and earliest from bronchogenic carcinoma. The clubbing also is consistent with this diagnosis. While the tumor could conceivably be primary in the heart, say, a sarcoma with spread to involve the pericardium as in a case reported by Brandenburg and Edwards from the Mayo Clinic, a far more likely possibility is that the tumor is secondary from, as indicated, a primary bronchogenic tumor.

If we are dealing with metastases to the heart, is the picture that of heart failure from extensive myocardial involvement? This may occur but is rare. That is, just the metastases to the heart muscle with enough muscle damage to produce failure would be rare. Myocardial involvement from metastases is said by some to involve more commonly the right heart. The picture here certainly seems to be predominantly of right-sided failure. However, there is disagreement on this point and, in any event, the clinical features are more those of interference with venous return to the heart than of heart muscle weakness or failure.

In that respect, I differ somewhat with the previous discussion. This suggests pericardial metastases. Such pericardial metastases could result either in a picture of constrictive pericarditis with the pericardial sac completely obliterated and the heart thoroughly encased, or of pericardial effusion, sanguinous or serosanguinous, with the ultimate development of a chronic tamponade.

In the first instance, namely, pericardial encasement of the heart, the heart is likely not to be enlarged. That is a picture of pure constrictive pericarditis with a normal sized heart which seemed to be the case here. Hence, the latter diagnosis is more likely, namely, neoplastic involvement of the pericardium, producing the effusion and tamponade.

The terminal event is quite consistent with this diagnosis. But why the temporary involvement after the first admission? That bothers me. I can only suggest that the pericardial involvement was at the time of the first admission sufficiently slight to allow for symptomatic relief by suitable therapy for the edema and hypervolemia. Short periods of improvement have been described in metastatic pericardial disease. Perhaps a period as long as this is not impossible.

The suggestive vectorcardiographic evidence of anterior wall myocardial infarction, in the absence of clinical evidence for such a diagnosis, raises the question of possible tumor involvement of the anterior myocardium. Incidentally, it is of interest to note that the highest incidence of tumor metastases to the heart occurs in malignant melanoma.

If the adenopathy is just misleading, that is, if the adenopathy, including that probably causing the esophageal deformity, is unrelated to the heart disease, other diagnostic possibilities must be considered. I refer to such conditions as valvular disease, either aortic or mitral, idiopathic hypertrophy, scleroderma, hemochromatosis, endocardial fibroelastosis and isolated myocarditis.

As to the valvular disease, there were no murmurs. Although aortic stenosis might occur in a man this age without a murmur, the absence of evidence of pulmonary congestion or considerable left ventricular failure and the absence of a murmur together would tend to exclude this possibility. The only finding to suggest mitral stenosis is the esophageal deformity. But this can be explained more satisfactorily in other ways. Idiopathic hypertrophy is usually found in young or middle aged adults. Also, the commonly occurring pulmonary embolization with infarction is not noted here.

There is no evidence of scleroderma, and if cardiac involvement preceded cutaneous or esophageal evidence, the diagnosis would not be possible. Also, the predominant right sided failure would be unusual.

There is nothing to suggest hemochromatosis, and as to endocardial fibroelastosis, the rather rapid course, the absence of evidence of embolization and the age of the patient would tend to discount this diagnosis, although cases have been reported in this age group.

The rather long and remittent course is unusual though not impossible in isolated myocarditis. I am not ruling that out as a diagnostic possibility.

The course was too rapid and the patient too old for the onset of symptoms from simple constrictive pericarditis.

I return then to the belief that the most reasonable explanation for the events as described is metastatic carcinoma involving the pericardium and possibly the heart. The primary lesion is probably bronchogenic carcinoma although the stomach or pancreas could conceivably have been the seat of the primary tumor.

*Dr. Hans Popper\**: We are confronted here with a patient who at the time of autopsy had extensive pitting edema. About 50 ml of fluid was in the peri-

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cardium and more than 1000 ml in each pleural cavity. Both lungs were emphysematous and, particularly in the left lung, sclerosis of the pulmonary artery and small areas of infarction were present. A thrombus, probably an embolus, was in the process of being organized in one of the branches of the pulmonary artery (Fig. 2). As the result of this obstruction which was found in a number



FIG. 2. Thrombus (arrow) in branch of left pulmonary artery with infarction of segment of lung.

of arteries, infarcts were noted. The moderate degree of sclerosis in the pulmonary artery branches suggested that at least at the time of death some degree of pulmonary hypertension should have been present. We suspected that some vascular changes were present either as a result of showers of emboli into the vessels or as a result of local vascular changes. As we inspected the vessels, we saw in the pulmonary arterial branches areas where there was an obvious interruption of the normal structure with some material being deposited in the wall. Another lesion present of little significance was an old tuberculous focus which failed to show any evidence of activation. In a regional lymph node some



recent reactivation was noted (Fig. 3). There was also a peculiar alteration of the stroma of these lymph nodes. It was thickened, and we consider this as evidence of globulin imbibition of the stroma, or hyalinosis, possibly the result of a local antigen-antibody reaction. This is an extremely common, uninteresting lesion, and I do not think it gave us much information as to the underlying disease.

The heart weighed 670 grams, a considerably enlarged organ. The pericardium was normal and no constrictive pericarditis was present. There was considerable hypertrophy and only slight dilatation of the right chamber of the heart with a mural thrombus in the appendage of the right atrium, which was moderately, but not significantly enlarged. The left ventricle showed considerable hypertrophy but not quite as marked as on the right side. The cusps of

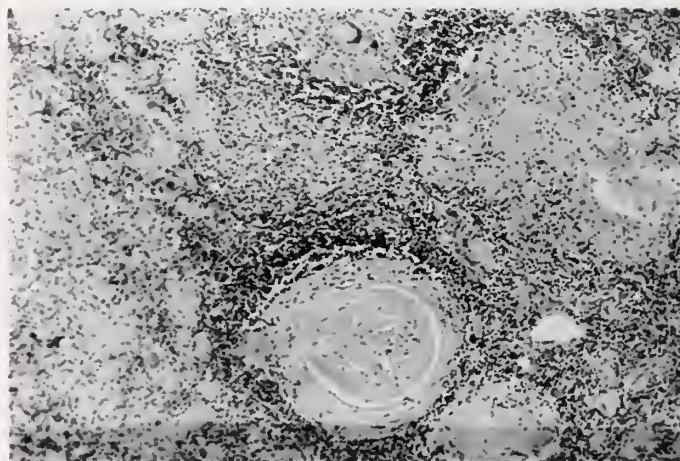


FIG. 3. Hilar lymph node with reactivation of old tuberculous focus. (H & E  $\times 40$ )

the aortic valve appeared normal, the mitral valve was slightly thick but not deformed with very delicate chordae tendineae, excluding a rheumatic etiology of the cardiac lesion. Irregular thickening was noted in some areas of the mitral valve but this did not interfere with function and was not atherosclerotic in nature. The myocardium was thickened and entirely homogeneous. There was nothing in this rather firm myocardium which suggested that inflammatory infiltration was present. In addition to the firmness and the rigidity of the organ, we noted severe hypertrophy and moderate dilatation of both chambers without sclerosis of the aorta or the coronary arteries which were indeed entirely normal as predicted. Histologically the original myocardial fibers were well preserved strands separated by reddish appearing material which accumulated around somewhat dilated but in no way obstructed coronary arterioles. This material diffusely invading the heart muscle took the specific Congo red stain which is characteristic for amyloid. Other metachromatic stains showed that part of the amyloid gave a positive reaction whereas other parts were not as distinctly stained. It did not interfere with the reticulum and no fibrosis had taken place.

It did interfere with the nutrition of the muscle cells which became atrophic (Fig. 4), partly lost their cross-striations and accumulated fat (Fig. 5). We had then a peculiar combination of hypertrophy of individual fibers with

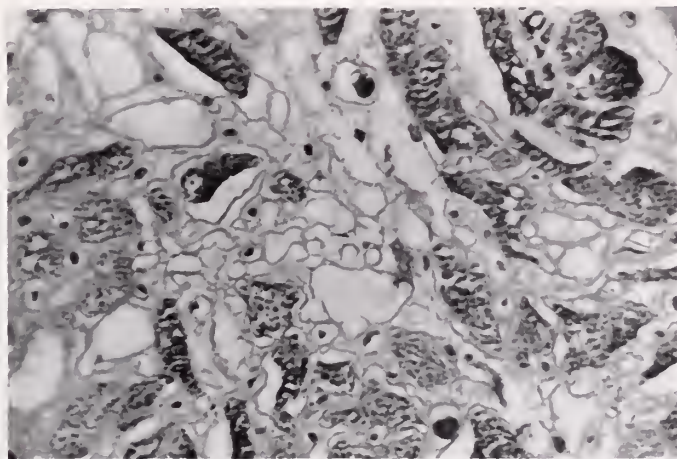


FIG. 4. Material deposited between myocardial fibers apparently crowding them out and encasing individual cells as in pericarditis. (Trichrome  $\times 40$ )

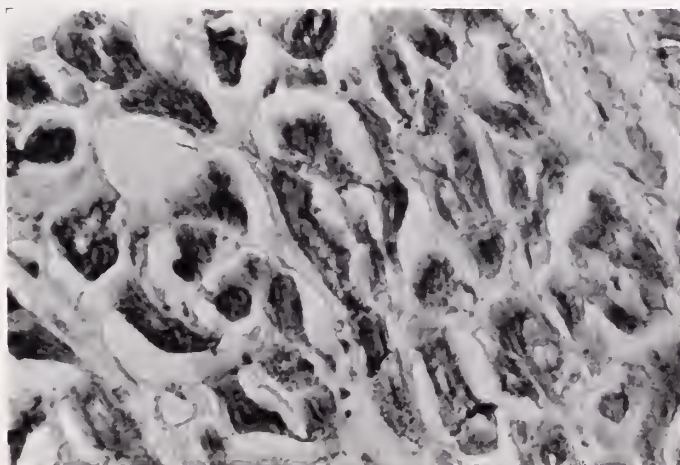


FIG. 5. Fat accumulation in anoxic myocardial fibers. (Oil red O  $\times 40$ )

atrophy and disappearance of others, producing this tremendous enlargement of the heart. The lesion crept below the epicardium into the area where the conducting system should be located and produced the conduction interference which the second electrocardiogram indicated. The left atrium was dilated and contained the mural thrombus of which we were informed before (Fig. 6) which was becoming organized (Fig. 7). In the myocardium of the atrium, a large amount of amyloid was deposited. Presumably this interfered with some of

the vessels leading to obstruction, infarction of the atrial myocardium with necrosis, and then a thrombus.

Several questions still remain to be answered. One is the arterial changes in the lung. Some were from showers of very small thrombi, only a few associated with infarction. Others resulted from amyloidosis of the pulmonary arterial branches producing pulmonary hypertension terminally.

The liver was small, weighing only 1,000 grams. Its edge was sharp and grossly no evidence of amyloid was seen. On the cut surface it showed a moder-



FIG. 6. Greatly dilated left ventricle with mural thrombus in auricular appendage (arrow) explaining compression of esophagus. Note slight thickening of mitral valve leaflets and normal chordae tendinae.

FIG. 7. Organizing thrombosis in left auricle. (H & E  $\times 40$ )

ate degree of passive congestion. Microscopically the passive congestion produced by cardiac failure was quite clearly indicated and amyloid accumulated around the vessels (Fig. 8). Combined congestion and this vascular interference led to the evidence of hepatocellular failure and accumulation of bile pigment with the slight degree of jaundice mentioned in the history. We saw this same vascular amyloidosis in other organs. In the adrenals severe vascular changes developed with retention of amyloid in the adrenal arteries and peculiarly enough even in the adrenal veins. There was no clinical evidence for adrenal insufficiency.

The kidneys showed infarcts which we would expect to find in the presence of the left auricular thrombosis. There was slight nephrosclerosis with altera-



tion of glomeruli. No amyloid was found. Grossly, the pancreas was normal but microscopically there was amyloid in the pancreatic vessels. Hemorrhagic areas were present in the small intestine with amyloidosis of the vessels which prob-

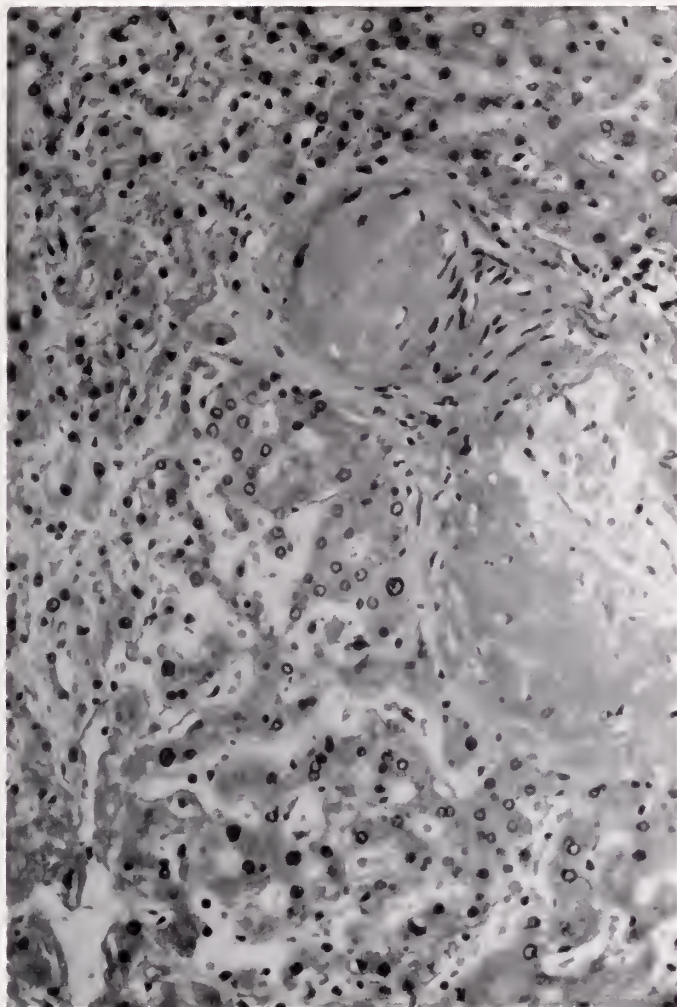


FIG. 8. Amyloidosis of hepatic artery branch with severe narrowing of the lumen. The parenchyma shows passive congestive. (Methyl-violet  $\times 120$ )

ably accounted for the changes. We could not examine the bumps on the hard palate but in the larynx as well as in the tongue amyloid accumulation was seen and we assume from this that amyloid deposits were in the hard palate. Vessels were moderately involved as well as muscles. Between the skeletal muscles there was arterial involvement as well as involvement of the interstitial tissue which had "imbibed" amyloid which oozed out around the vessels.

The last problem confronting us was the etiology of the amyloidosis (2-5).



Of the various abscesses, perirectal and others, at the time of the autopsy, we could not find anything. They must have been rather small, and they had healed. I am very hesitant, just as Dr. Blumgart and Dr. Proger were, to connect

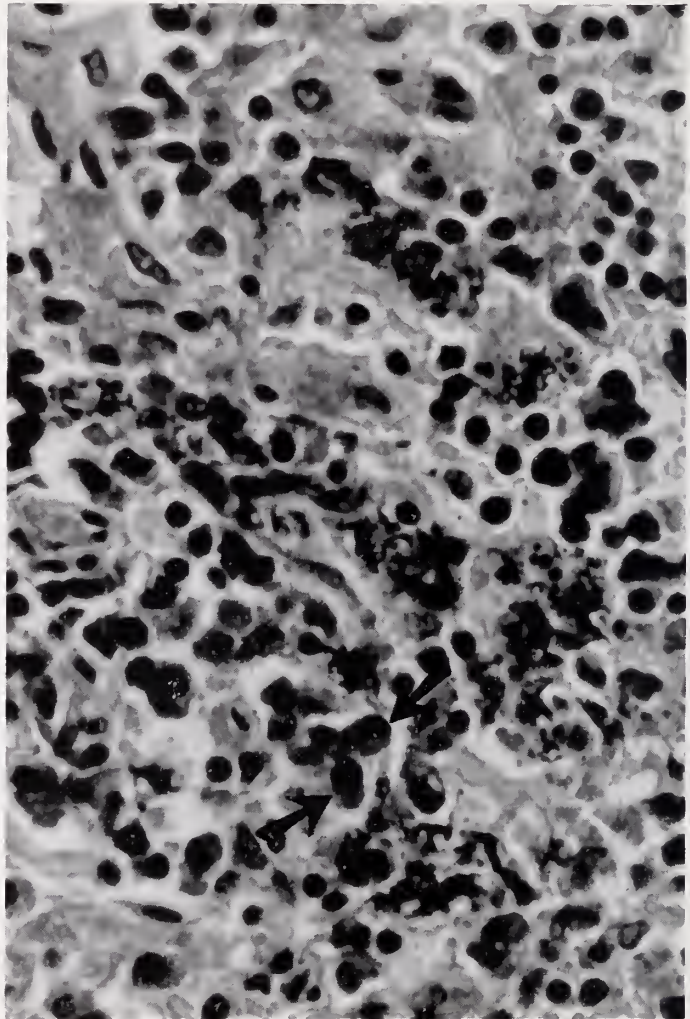


Fig. 9. Increase in plasma cells (arrows) in lymph node. (H & E  $\times 320$ )

amyloidosis here with chronic suppuration, especially since pus was absent and tuberculosis was borderline and most probably not related. In my own experience of a few cases of cardiac amyloidosis, either a myeloma was present, unrecognized clinically and detected at autopsy, or at least plasmacytosis of the bone marrow was found. We were not permitted to investigate all bones but the one we studied was free of myeloma. The bone marrow was normal as we would predict it to be with the normal peripheral blood counts. The search for plasma

cells revealed a few. The lymph nodes, however, were enlarged. In the larger nodes there was some irregularity of the architecture and plasma cells were increased in number (Fig. 9). The spleen was especially impressive. Grossly it looked normal in size and appearance and microscopically it showed congestion which was not too significant. On high power examination, plasma cells could not be demonstrated until we did a pyronine stain, and this showed a large number of mesenchymal cells, rich in pyronine staining cytoplasm, which resembled plasma cells. We designated them plasmaeytoid cells and we know from other cases that large amounts of gamma globulin are found in these cells which therefore correspond to plasma cells in their significance. We have then a condition in which plasmaeytosis in the lymph node and plasmaeytosis in the spleen led to primary amyloidosis in the heart. I feel that the perirectal abscess and buttock abscess were a result of an altered immunologic response associated with the lesion rather than its cause. I have yet to see primary amyloidosis of the heart in which thorough examination does not reveal increased plasmaeytes and plasmaeytoid cells. As characteristic in primary amyloidosis, no hepatosplenomegaly was present. We have to assume that 11 months before death, the myocardial fibers were involved, with resulting dyspnea, edema, gallop rhythm, rising venous pressure and circulation time and albuminuria.

#### Final diagnoses:

1. Primary amyloidosis of the heart and blood vessels.
2. Mural thrombus of left atrium.
3. Multiple small pulmonary emboli.
4. Plasmaeytosis of spleen and lymph nodes.

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# *Radiological Notes*

BERNARD S. WOLF, EDITOR

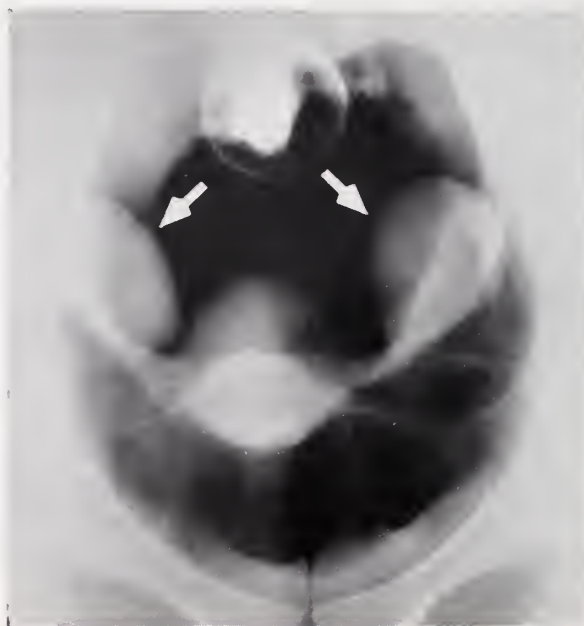
## *Gynecologic Radiology*

RICHARD H. MARSHAK, M.D., AND CLAUDE BLOCH, M.D.

*New York, N. Y.*

### CASE NO. 136

This was the first admission of a 19 year old female. Her menses started at the age of 14, occurring every 30 days, were scant and lasted only three days. Over the next few years, her menses gradually became even scantier until finally during the last two years, she had total amenorrhea. She had noted a mild growth



Case 136, Fig. 1. The uterine outline is normal in size, shape and position. Both ovaries (arrows) are slightly enlarged with smooth contours.

of facial hair and had gained approximately twenty pounds during the last year. Physical examination revealed a normal sized uterus. There was slight

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

fullness in both adnexal regions. Urinary 17 keto-steroids were slightly increased.

A gynecogram (Fig. 1) was performed and revealed the following: The uterine outline was normal in size, shape and position. Both ovaries were slightly enlarged with smooth contours. The findings were consistent with the diagnosis of the Stein-Leventhal syndrome.

At operation, the ovaries were noted to be enlarged. The capsule was thickened and numerous microcysts were identified. A wedge resection of both ovaries was performed.

*Comment:* The pathology of this disease has not been clearly elucidated but usually there is bilateral enlargement of the ovaries with thickened capsule and multiple microcysts. On occasion, the enlargement has been reported to be unilateral. The treatment has consisted in most cases of wedge resection. Why this should be of benefit, nobody knows. Exact measurements for enlargement of the ovary are not available. However, this is usually determined by comparison with the size of the body of the uterus. When the ovaries are larger than the body of the uterus, they are considered to be abnormal.

*Technique:* Gynecography is performed by introducing approximately 1000 to 1500 cc of carbon dioxide into the peritoneal cavity via the cervical canal. Films are taken with the patient prone and in 35 degrees Trendelenberg. One film is taken in the straight frontal projection, one with 5 degrees tilt of the x-ray tube toward the head and one with 5 degrees tilt toward the feet. Soft tissue technique is employed.

*Case Report:* STEIN-LEVENTHAL SYNDROME.

#### CASE NO. 137

A 46 year old woman consulted a gynecologist because of continued mild vaginal bleeding of four weeks duration. Her past history was unremarkable. The patient's menses had ceased at the age of 42 and she had no bleeding until the present illness. Physical examination was normal except for the pelvic findings which revealed a slightly enlarged and boggy uterus. A hysteroqram revealed a slightly enlarged uterine cavity with an irregular mass in its superior half. The impression was carcinoma of the uterus.

*Comment:* The question whether to perform a hysteroqram in the presence of post-menopausal bleeding has been discussed for a long time. Because of the possible retrograde dissemination of cancer cells in these cases, it is important to inject only enough radiopaque material to delineate the lesion and to avoid filling the tubes. However, in many centers, hysteroqram is performed routinely to determine the size and position of a carcinoma of the uterus.

In the post-menopausal period, any irregular filling defect within the uterus is suspicious of carcinoma. In young patients, however, irregular defects are often due to retained placental remnants and on occasion represent endometrial hyperplasia. In these cases, the contours of the uterine cavity can usually be delineated and are intact. In some instances, where the walls are not distinctly outlined, the differential diagnosis is in doubt. On occasion, a carcinoma of the





Case 137, Fig. 1. The uterine cavity is slightly enlarged with an irregular mass in its superior half.

uterus presents as a smooth intraluminal filling defect, simulating an endometrial polyp.

*Case Report:* CORPUS CARCINOMA OF THE UTERUS.

#### CASE NO. 138

R. P., a 27 year old nullipara was first seen in May 1959 complaining of irregular bleeding, occasionally profuse with clots. Her menses started at the age of 13 and until the present illness occurred every 30 days, lasting 6 days. Treatment had consisted mainly of hormones administered by mouth without any effect. Physical examination revealed no evidence of any abnormality except for the pelvic findings. The cervix was eroded. The uterus was not enlarged but was retroverted. In June 1959, a diagnostic curettage was performed and a small amount of tissue was obtained. No irregularity of the uterine cavity was noted. Microscopic examination revealed proliferative endometrium and the patient was discharged in good condition. Two weeks later bleeding again started. Ergotrate was administered with slight diminution of the bleeding. After three months of intermittent spotting, a hystero-gram was obtained (Fig. 1). This showed the uterine cavity to be globular in outline, retroverted and normal in size. A filling defect occupied the entire cavity and a presumptive diagnosis of a submucous fibroid was made. One week later, the patient was prepared for vaginal hysterotomy. Prior to this operation, a second diagnostic curettage again revealed no evidence of an intrauterine lesion. When the cervix was incised and a finger introduced into the uterus, a submucous fibroid the size of a walnut was detected.



Case 138, Fig. 1. The uterine cavity is globular in outline, retroverted and normal in size. There is a smooth filling defect occupying the entire uterine cavity.



Case 138, Fig. 2. Typical example, in another patient, of a submucous fibroid. The uterine cavity is enlarged and globular containing a large smooth filling defect.

It was attached to the posterior wall by a broad pedicle. This was excised and the patient made an uneventful recovery.

Figure 2, of another patient, shows the typical appearance of a submucous fibroid. There is an enlarged, globular uterine cavity containing a large, smooth filling defect.

*Comment:* Submucous fibroids may be small or large, single or multiple. They usually enlarge the uterine cavity, the degree depending upon the size of the tumor. When the uterine cavity is enlarged, it is usually globular in outline. When small, the submucous fibroids are impossible to differentiate from endometrial polyps. An intrauterine pregnancy can completely simulate the findings associated with a submucous fibroid. An adenomyotic nodule can, on rare occasions, produce similar findings to that described above. The above case demonstrates the most important indication for the performance of a hystrogram, that is, menometrorrhagia in a young female with a slightly enlarged, globular uterus. It is not unusual for the gynecologist to overlook the tumor with a curette because of the smooth surface of the uterine fibroid.

*Case Report:* SUBMUCOUS FIBROID.

#### CASE NO. 139

A.K. was a 38 year old nullipara complaining of prolonged menstrual bleeding for the last twelve months. Her past history was normal. Physical examination



Case 139, Fig. 1. The uterine cavity is normal in size, shape and position. There are many small sac-like projections extending from the contours of the uterine lumen.

revealed a slightly enlarged uterus. A hystrogram (Fig. 1) revealed the following: The uterine cavity was normal in size, shape and position. Many small projections with an irregular sac-like configuration were seen extending from the contours of the uterine lumen. Some of the radiopaque material entered the left tube. The right tube was not visualized. The roentgen appearance was characteristic of adenomyosis of the uterus.

*Comment:* The most striking diagnostic feature is the demonstration of short

spicules or sac-like structures extending perpendicularly from the borders of the uterine cavity, varying in length from one to four millimeters. On occasion, the spicules are elongated, measuring from one to two centimeters in length and presenting a circuitous or undulating course. Although branching is seen occasionally on microscopic sections, it is rarely noted on the hystrogram.

The above finding is demonstrated in approximately one third of the patients with adenomyosis. In the remaining patients, there are no alterations to suggest the diagnosis.

*Case Report: ADENOMYOSIS.*

#### CASE NO. 140

L.T., a 17 year old nullipara was seen with the chief complaint of irregular bleeding for the last two years. Her menses started at the age of 14 and occurred



Case 140, Fig. 1. There is a complete bicornuate uterus. Within the midportion of the right horn of the uterine cavity there is a smooth circular filling defect measuring approximately 1 cm in diameter.

every thirty days, lasting four days. Because of the bleeding, the patient underwent a dilatation and curettage which revealed no evidence of any abnormality within the uterine cavity. Microscopic examination of the tissue showed proliferative endometrium. Bleeding continued and a course of steroid therapy was suggested. After four months of androgenic hormones, hirsutism was noted. Despite this, hormones were continued because of uninterrupted bleeding. The hirsutism became worse and the hormones were finally terminated. Dilatation and curettage was performed again with no evidence of any abnormality.

The patient consulted another gynecologist who suggested a hystrogram. Hystero-graphy (Fig. 1) revealed the presence of a complete bicornuate uterus. Within the midportion of the right horn of the uterine cavity, there was a smooth circular filling defect, measuring approximately 1 cm in diameter. A dilatation



and curettage of the right horn was performed with removal of the polyp. This was followed by complete cessation of the patient's abnormal bleeding.

*Comment:* This case is of unusual interest because of the repeated curettages, the continued bleeding, the administration of androgenic hormones and the subsequent roentgen findings. The operator was unaware of the presence of the bicornuate outline of the uterus and the left horn of the uterine cavity only was curetted. The hystrogram in this case was of inestimable value in revealing the true nature of the findings.

On occasion, a bicornuate uterus is demonstrated in a patient who has had repeated miscarriages. Correction of this type of abnormality with removal of the body of muscle between the two horns of the uterine cavity is occasionally feasible. In the absence of operation, hystero-graphy is frequently the only way of confirming the presence of a congenital anomaly. Endometrial polyps are a frequent cause of bleeding. They usually do not deform the normal configuration of the uterine cavity and characteristically are smooth, but may be irregular.

*Case Report:* ENDOMETRIAL POLYP WITH BICORNUATE UTERUS.

#### CASE NO. 141

L.S., a 28 year old female, consulted a gynecologist because of inability to become pregnant during a period of six years. The past history and physical ex-



Case 141, Fig. 1. The uterine cavity is situated slightly to the right of the midline and is normal in size and shape. The left tube is not visualized. The distal third of the right tube is moderately dilated and club-shaped with no evidence of patency.

amination were completely normal. A Rubin test demonstrated closure of both tubes and a uterosalpingogram (Fig. 1) was performed to determine the point of closure. The uterine cavity was situated slightly to the right of the midline and was normal in size and shape. The left tube was not visualized. The distal third of the right tube was moderately dilated and club-shaped with no evidence of any patency. Immediately proximal to the dilated segment, the contours of the right tube were irregular and the mucosa appeared to be ulcerated. The impression was tuberculous salpingitis with closure of the fimbriated end of the right tube.

*Comment:* Hysterosalpingography is invaluable for the demonstration of patency of the tubes. Not infrequently, a Rubin test will indicate the presence of closed tubes when a uterosalpingogram discloses normal patent tubes. This is probably due to the fact that larger pressures are employed with hysterosalpingography than with the Rubin test. When using higher pressures, water soluble material is preferable to oil. Closure of a tube at the cornual end should be viewed with circumspection as this can be a transient phenomenon related to spasm and not necessarily due to an organic lesion. In the above case, there was a hydrosalpinx of the right tube. The presence of tuberculosis was suggested by ulceration of the mucosa and irregularity of the contours. On occasion, sinus tracts or even calcific deposits can be demonstrated. Alternating areas of narrowing and dilatation of the distal portion of the tubes are highly suggestive of tuberculosis.

*Case Report:* TUBERCULOSIS SALPINGITIS.

#### CASE NO. 142

L.P., age 32, was first seen in October 1959 with the chief complaint of vaginal bleeding of two weeks duration. Her past history was unremarkable. Her menses started at the age of 13, occurring every 28 days. Her last period was three months prior to admission and lasted only three days. The flow, however, was no different than during previous periods. Two weeks before admission, she began to bleed continuously. There was no abdominal discomfort. She was para I, gravida I. Physical examination was entirely negative except for the pelvic findings. The cervix was soft. The uterus was not enlarged and was in the midline. Neither adnexa could be palpated but slight tenderness was elicited in the left adnexal region. A pregnancy test was negative. Curettage produced proliferative endometrium. The patient continued to bleed vaginally following the curettage and a hystrogram (Fig. 1) was performed.

The radiographs revealed the uterine cavity to be normal in size and shape. The left tube revealed no evidence of any abnormality and was patent. The distal end of the right tube had a trumpet-like appearance. Within this region, there was a filling defect approximately the size of a walnut. The diagnosis was tubal pregnancy.

*Comment:* Ectopic pregnancy is occasionally diagnosed on roentgen examination. The appearance described above is typical. This consists of a trumpet-like



Case 142, Fig. 1. The uterus is normal in size, shape and position. The distal end of the right tube has a trumpet-like appearance. Within this region, there is a filling defect approximately the size of a walnut. The left tube is normal.

configuration of the distal end of the tube. This is due to the ectopic mass lying within the leaves of the fimbria. We have usually not performed hysterocontrast pyelography in cases of suspected ectopic pregnancies. In our experience, the diagnosis has usually been an incidental finding.

*Case Report:* ECTOPIC TUBAL PREGNANCY.

# Abstracts

## *Papers Presented Before the Research Club of The Mount Sinai Hospital*

*New York, N. Y.*

*The Role of the Ductular Cell in Bile Formation.* Edward J. Singer, Ph.D., Stanley Goldfarb, M.D., Tibor Barka, M.D., and Robert Pang, M.D. (From The Department of Pathology, The Mount Sinai Hospital, New York).

Rate of flow and composition of bile, and serum bilirubin were studied in the rat during chronic ethionine and  $\alpha$ -naphthylisothiocyanate (A.N.I.) intoxication to investigate the relation of the conspicuous ductular cell proliferation characteristic of these intoxications to the bile secretion and thus elucidate the role of the ductular cell in bile formation.

Ethionine feeding for six weeks produced diffuse single cell necrosis of liver cells and extensive proliferation of ductular cells. The rate of bile secretion increased from a control level of 0.6 ml per hour to 2.3 ml per hour. Whereas the rate of excretion of biliary solids was increased, the production of bile acids, which normally constitute 40 per cent of bile solids was decreased. Bilirubin content was very low, despite high serum bilirubin. Rose bengal clearance was reduced and the ratio of trihydroxy to dihydroxy bile acids was reversed from 2:1 to 1:2.

A.N.I. feeding produced intrahepatic biliary obstruction by necrosis of bile ducts with plugging. During the second week bile flow stopped but later as ducts regenerated and obstruction was relieved, bile flow increased reaching a peak at seven weeks with a parallel increase in bile bilirubin. By 20 weeks the bile flow fell from 4 times normal and bilirubin excretion from 6 times normal, to normal levels; the fall of bile flow preceding the decrease in bilirubin excretion. At this time the liver showed extreme ductular cell proliferation.

The results are reconcilable with the assumption that the ductular cells contribute to bile production, probably by regulating water content.

*The Detection of ABO Isoagglutinins Related to Erythroblastosis.* Shaul Kochwa, Ph.D., Richard E. Rosenfield, M.D., and Lisa Tallal, M.D., (From The Department of Hematology, The Mount Sinai Hospital, New York).

A method has been developed for the prenatal detection of ABO isoagglutinins that are related to erythroblastosis. All forms of erythroblastosis are dependent upon maternal isoagglutinins which pass the placental barrier and unite with the erythrocytes of the fetus, but in the case of ABO incompatibility the competitive neutralizing effects of ABO antigens found in the secretions and tissues of the fetus require equal and simultaneous consideration.

ABO isoagglutinins which sediment 7S globulins can be separated on DEAE cel-



lulose columns. These antibodies were demonstrated to occur in equal titer in the paired sera obtained at delivery of mothers and their ABO compatible newborn. Most maternal isoagglutinins were encountered in those column fractions which contained 19S  $\gamma$  globulins, but cord serum isoagglutinins were recovered only in 7S  $\gamma$  globulin fractions.

Of 110 prenatal sera tested, 7S isoagglutinins were not encountered in all of 28 type A and 9 type B mothers, but were found in 53 out of 73 type O mothers ten of whom possessed specific titers of 1:20 to 1:160 and delivered ABO incompatible newborn. When tested for resistance to inhibition by specific soluble blood group substances (hog A and horse B), only five of 73 type O mothers were found to have noninhibitable 7S isoagglutinins. Four of these mothers delivered type O children, but one delivered a type B child. This was the only newborn of the series to have ABO erythroblastosis, and exchange transfusion therapy was required.

Six other women with a history of having had one or more children with severe ABO erythroblastosis, and five unselected donors who had been immunized with specific soluble blood group substances, were tested in the same fashion, and all were found to have noninhibitable 7S isoagglutinins of the proper specificity.

The column chromatographic separation of 7S isoagglutinins offers a new approach to study isoimmunized mothers, especially primagravida, for estimation of the severity of erythroblastosis to be expected.

Theoretical considerations will be discussed.

*Studies in Visceral Arteriography.* Murray W. Seitchik, M.D., Marvin Poll, M.D., Eugene L. Komrad, M.D., and Ivan D. Baronofsky, M.D.

A technique for the high contrast visualization of major visceral aortic branches by retrograde femoral aortography was studied. The method entailed passage of a suitable catheter into the aorta by means of a femoral arterial cut-down. The tip of the catheter was localized in the region of the coeliac artery by means of roentgenograms. A film was then taken during the rapid injection of 30 milliliters of 50% hypaque. The method was specifically utilized in order to identify the hepatic artery and its branches in the dog. In 28 arteriograms performed on 18 dogs, good visualization of the hepatic artery and its branches was consistently attained. The superior mesenteric artery was also well demonstrated by this procedure. In an investigation of the effects of hepatic artery ligation in the normal and experimentally ascitic dog, this technique was utilized to verify the arterial ligation and demonstrate any collateral circulation that developed.

In a series of ten dogs in which the hepatic artery had been ligated near the coeliac axis, there was a survival rate of 80 per cent without antibiotics. No significant difference was noted between the normal and ascitic animals. In another series of eight dogs, the right and left hepatic end arteries were ligated and divided at the porta hepatis resulting in a 25 per cent survival without antibiotics. The site of ligation of the hepatic artery was easily identified with this angiographic method. In all of the animals that survived hepatic artery ligation at

the porta hepatis, it was possible to demonstrate persistent hepatic arterial blood supply.

The technique of retrograde femoral aortography is well documented in the literature. This investigation verifies its relative simplicity and reliability. In view of recent reports in the literature of correctable arterial defects, application of this procedure in man for recognition of pathology of the visceral aortic branches appears warranted.

*The Localization of Acid Phosphatase Activity In The Golgi Zone Of Endocrine Organs, And Its Relation To Secretory Activity.* Harold John Sobel, M.D. (From the Department of Pathology, Trainee in Experimental Pathology, U. S. P. H. S. This investigation was supported by U. S. P. H. S. Graduate Training Grant 2G-115.)

A modified azo-dye coupling technique with improved localization enabled a high acid phosphatase activity to be invariably observed in endocrine organs. The dye deposit was superimposed upon the negative image of the Golgi zone in the pituitary basophil and was also noted in locations similar to that of the Golgi apparatus in other endocrine cells. It is known that the Golgi zone of endocrine organs increases in size and complexity in states of increased secretory activity and, conversely, assumes a smaller and simpler structure with diminished activity. In an effort to determine the functional significance of acid phosphatase in secreting organs, this enzyme was studied histochemically and chemically (quantitatively) in the thyroid and anterior pituitary glands of the rat. The hormonal activity of these organs was influenced by cold, castration; and the administration of thyroxine, testosterone and growth hormone. Under these conditions of stimulation and inhibition a parallelism between the expected level of hormonal production and histochemical acid phosphatase activity was found in all cells studied (pituitary thyrotrophs, gonadotrophs, and acidophils, and thyroid acinar cells). This relationship could be confirmed chemically for the thyroid acinar cells but not for the pit cells because of the heterogeneity of the pituitary gland. The study suggests a possible physiologic relationship between the Golgi zone acid phosphatase and hormone production.

*Lipoprotein Lipase in the Exocrine Secretion of the Pancreas.* Jacques Kessler, M.D., Martin Finkel, M.D., and Henry D. Janowitz, M.D. (The Mount Sinai Hospital, New York, N. Y.)

Since transient hyperlipemia occurs at times in experimental and spontaneous pancreatitis, pancreatic juice was examined for clearing factor, lipoprotein lipase. Juice was obtained from mongrel dogs through a Thomas fistula, stimulated by secretin and pancreozymin and examined for lipolytic activity in an activated lipid buffer solution (cotton seed oil, albumin, phosphate buffer, pH 8.5) designed for the determination of lipoprotein lipase. This was repeated with inhibitors of lipoprotein lipase (protamine sulfate 20 mg./cc and 5% Na taurocholate) and pancreatic lipase (1M Na fluoride). The juice was subjected to a standard technique for purification of lipoprotein lipase: adsorption by  $\text{Ca}_3(\text{PO}_4)_2$  gel and elution with Na citrate. Lipolytic activity was demonstrated after secretin and

pancreozymin. Concentration was inversely related to rate of secretion following secretin, while pancreozymin augmented the concentration of lipolytic activity. This was diminished by specific inhibitors of lipoprotein lipase, and by an inhibitor of "classical" pancreatic lipase. With  $\text{Ca}_3(\text{PO}_4)_2$  gel adsorption significant lipolytic enzyme was recovered. The findings suggest that pancreatic juice contains lipoprotein lipase activity in addition to "classical" pancreatic lipase. Similar activity was observed in pancreatic tissue extracts.

*Symptomatic Hyperserotoninemia (Without Carcinoid) Associated With Diminished Urinary Excretion of 5-HIAA.* Richard R. Pichel Warner, M.D. (From the Department of Medicine, Division of Gastroenterology).

Nausea, vomiting, abdominal cramps, and diarrhea can be caused by hyperserotoninemia as occurs naturally in the functioning carcinoid syndrome, or following administration of large amounts of 5-HTP. In both instances an increased urinary excretion of 5-HIAA occurs. Study of many patients having symptoms suggestive of hyperserotoninemia disclosed seven individuals having increased blood 5HT associated with subnormal urinary 5-HIAA. Of five of these patients given 5HT p.o., four excreted subnormal amounts of urinary 5-HIAA. This in addition to the findings of other chemical studies, suggests the possibility of an aberration in 5HT metabolism associated with diminished monoamine oxidase activity.

Duration of symptoms in these patients ranges from two to twenty-three years. All have had multiple diagnostic studies in the past without the disclosure of organic disease. Clinical characteristics of this syndrome consist of abdominal pain, nausea and vomiting, diarrhea, weight loss, weakness, and easy fatiguing, increased gastric secretion (as demonstrated by x-ray), and possibly psychiatric disturbances. One patient of the group also experiences flushes. All of these patients have recurrent episodic attacks, but most have some or all of their complaints to a lesser intensity between attacks. A provocative test consisting of the I.M. administration of reserpine was performed in four patients of the group and in each produced a severe typical attack of abrupt onset. Therapy with an experimental antiserotonin produced distinct improvement in those patients of the group able to tolerate the drug.

*Potassium in Mecholyl-Stimulated Gastric Secretion.* J. Lawrence Werther, M.D.,\* and Franklin Hollander, Ph.D. (From the Gastrointestinal Physiology Research Laboratory and the Division of Gastroenterology, Department of Medicine, The Mount Sinai Hospital, New York.) Presented February 13, 1961.

Previous investigations have indicated that potassium concentration  $[\text{K}]$  of gastric juice rises abruptly following the onset of histamine-stimulated secretion.

It had been suspected that this K efflux results from a direct action of the injected histamine upon cell membrane permeability to K, since this phenomenon has been observed with other mammalian tissues.

In 26 experiments using Heidenhain and vagal pouch dogs the effects of mecholyl injection on  $\text{K}^+$  and  $\text{H}^+$  concentration and output and on rate of secre-

tion were determined and compared to the effects of histamine in the same dogs. The pattern of  $[K]$  and  $K$ -output time-curves following mecholyl were similar to the patterns following histamine. Although  $[K]$  may rise initially after mecholyl, this rise tended to be of smaller magnitude and occurred less consistently than the rise following histamine. After both stimuli  $[K]$  ultimately falls below baseline levels after which there is recovery of the basal level. Acid secretion after either stimulus is accompanied by efflux of  $K^+$  into the gastric lumen. The output of  $K^+$  and the output of acid are closely correlated, whereas  $[H^+]$  and  $[K^+]$  are not correlated.

It is concluded that histamine administration is not essential to the  $K$ -efflux of acid secretion.  $K$ -efflux may represent a more basic process associated with neuroglandular stimulation or with the mechanisms underlying HCL secretion itself. [\*Supported by Grant A-2290, National Institutes of Health, U.S.P.H.S.; Trainee in Gastroenterology, U.S.P.H.S., Grant 2A-5126.]



# *Important Notice*

## T O S U B S C R I B E R S

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THE JOURNAL OF  
THE MOUNT SINAI HOSPITAL

ACQUIRED HYPOGAMMAGLOBULINEMIA AND SPRUE: REPORT  
OF A CASE AND REVIEW OF THE LITERATURENATHANIEL COHEN, M.D., DAVID PALEY, M.D.,  
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Since the first descriptions of the syndromes of congenital (1) and acquired hypogammaglobulinemia (2, 3), an increasing number of cases have been reported in the literature (4). Although diarrhea occasionally occurs in the congenital form (5), it is usually not a prominent feature of the clinical picture. In the acquired form, however, diarrhea, steatorrhea, or a "sprue-like" syndrome has been frequently mentioned. In a review of the literature, Zimneman and Hall stated that 6 of 32 patients with acquired hypogammaglobulinemia had steatorrhea (6). In a similar review, Cerf *et al.* tabulated 11 of 29 patients with diarrhea or a "sprue-like" syndrome (7). Gitlin *et al.* estimate the incidence at approximately twenty per cent of reported cases of acquired hypogammaglobulinemia (4).

When the individual case reports of patients having hypogammaglobulinemia and diarrhea or steatorrhea are scrutinized, the majority of cases are found to belong to the following categories:

(a) Known organic causes for diarrhea such as diverticulitis (8), staphylococcal enterocolitis (8), granulomatous disease of the intestinal tract (possibly tuberculosis) (6), recurrent pancreatitis (9), parasitic infestation (7), enlarged inflammatory intra-abdominal lymph nodes (10), and intra-abdominal lymphoma treated with alkylating agents and irradiation (11);

(b) Diarrhea present but not described as "sprue-like" and no evidence for sprue presented (11-13);

(c) Described as "sprue-like" but no evidence for sprue presented (14, 15).

In a careful review of the literature, we have been able to find only six cases of acquired hypogammaglobulinemia whose clinical description and laboratory studies were compatible with the diagnosis of sprue (3, 10, 16-19) and one of these [Case #1 of Rosecan *et al.* (10)] was believed by the authors to represent an unusual form of diffuse jejunoileitis in which the course was influenced by an altered response to infection. Characteristic histological findings in small bowel mucosal biopsies obtained by peroral suction have been recently reported in patients with nontropical sprue, celiac disease, and tropical sprue (20-22). None of the previously reported cases of hypogammaglobulinemia, however, have been studied in this manner. A patient with hypogammaglobulinemia who presents the clinical, laboratory, and histological evidence of sprue forms the basis for the present report.

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## CASE REPORT

A 19 year old white female was admitted to The Mount Sinai Hospital, August 15, 1957 for evaluation. She had lived in Venezuela all her life and had come to New York City for medical care. She was completely well until age 15 when she developed persistent diarrhea consisting of about six foamy foul-smelling liquid stools daily. In spite of this, she maintained her health and strength and was able to carry on her usual activities. One year later, she was found to have anebiasis and was treated with medications of an unknown nature. She subsequently was discovered to be anemic and, one year prior to admission, she developed ankle edema. She was treated with a great variety of drugs including folic acid, vitamin B<sub>12</sub>, various vitamin mixtures and antibiotics including tetracyclines. Her diarrhea improved so that just prior to admission she was having one or two formed, bulky, and foul-smelling stools daily. Her past history was unremarkable, with no unusual history of infections. Her appetite was good. There was no nausea, vomiting, fever, rectal bleeding, glossitis, weakness or abdominal pain. The family history was not remarkable.

The patient was well developed and well nourished. Blood pressure was 110/80 mm Hg. The skin was normal. There was no lymphadenopathy. Examination of the head, eyes, ears, nose, throat, neck, heart and lungs was normal. The spleen was palpable two fingerbreadths below the costal margin, smooth, firm, and nontender. Rectal examination was negative. There was minimal pitting edema of the lower extremities. Neurological examination was normal.

Hemoglobin, urinalysis, erythrocyte sedimentation rate, urea nitrogen, thymol turbidity, cephalin flocculation, serum electrolytes, calcium, phosphorus, alkaline phosphatase, prothrombin time, urine Sulkowitch test, basal metabolic rate, and electrocardiogram were all normal. The white blood count was 8050 per mm<sup>3</sup> with 63% polymorphonuclears, 28% lymphocytes, 5% monocytes, and 4% eosinophiles. First strength PPD was negative. Examination of the stools revealed endamoeba histolytica cysts and giardia lamblia as well as red and white blood cells. No enteric pathogens were found on culture. Barium enema examination demonstrated minimal functional changes on the postevacuation films. X-rays of the bones were normal.

Her serum proteins and parameters of intestinal absorption were investigated. Serum protein on two occasions by the Howe method were 6.4 and 6.7 Gm% with albumins of 4.6 and 4.6 and globulins of 1.8 and 2.1 Gm% respectively. Paper strip serum electrophoresis demonstrated a protein distribution of 81.1% albumin, 2.7% of alpha-1 globulin, 6.3% alpha-2 globulin, 8.1% beta globulin, and 1.8% gamma globulin (Fig. 1). A repeat serum electrophoresis was essentially unchanged. Chemical serum globulin distribution by the Greenspan technique (23) revealed a mucoprotein of 39 mg% (normal 49-70), an acid precipitable globulin turbidity of 2.2 units (normal 4-8), and a zinc sulfate turbidity of 1.0 units (normal 4-8).

Oral Vitamin A Tolerance Test	0 hrs. 46	4 hrs. 78	6 hrs. 113	8 hrs. 76	gamma %
Oral Carotene Tolerance Test	0 hrs. 27	48 hrs. 34	72 hrs. 37	192 hrs. 29	gamma %
Oral Glucose Tolerance Test	0 hrs. 63	$\frac{1}{2}$ hr. 107	1 hr. 115	2 hrs. 91	3 hrs. 70 Gm %

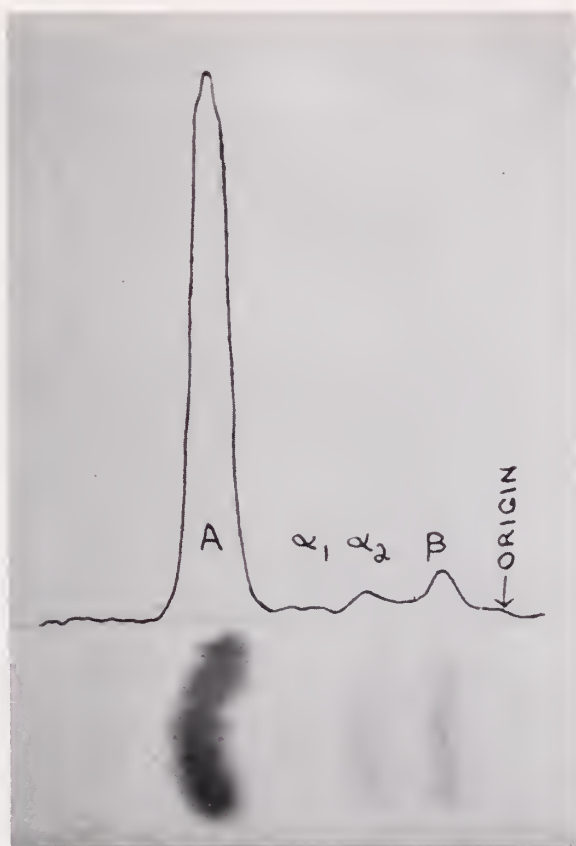


FIG. 1. Paper electrophoresis of serum stained with Amido Black and Analytrol scan of strip showing extremely faint band in the gamma globulin region.

Fecal fat just before discharge with the patient markedly improved was 2.64 Gm per 24 hours. Total plasma cholesterol was 115 mg% with 8 mg% esterified. Phospholipids were 144 mg% and total lipids 465 mg%. X-rays of the upper gastrointestinal tract and small bowel revealed dilatation of loops throughout the small intestine, with marked coarsening of mucosal folds, increased secretions, and segmentation and flocculation of the barium, consistent with the diagnosis of sprue (Fig. 2). Peroral jejunal biopsy with the Shiner tube revealed flattening and atrophy of the mucosa, marked diminution of the absorbing surface and increased cellularity in some areas (Fig. 3). Other areas showed a lesser



degree of atrophy with preserved villi, but severe changes in their finer structure. These villi were clubbed at their tips and many were in the process of fusion (Fig. 4). The changes are those seen in the primary malabsorption syndrome.

The patient was treated with enteric coated Vioform, 0.5 Gm twice daily for 12 days with eradication of the parasites from her stools. She was also placed on

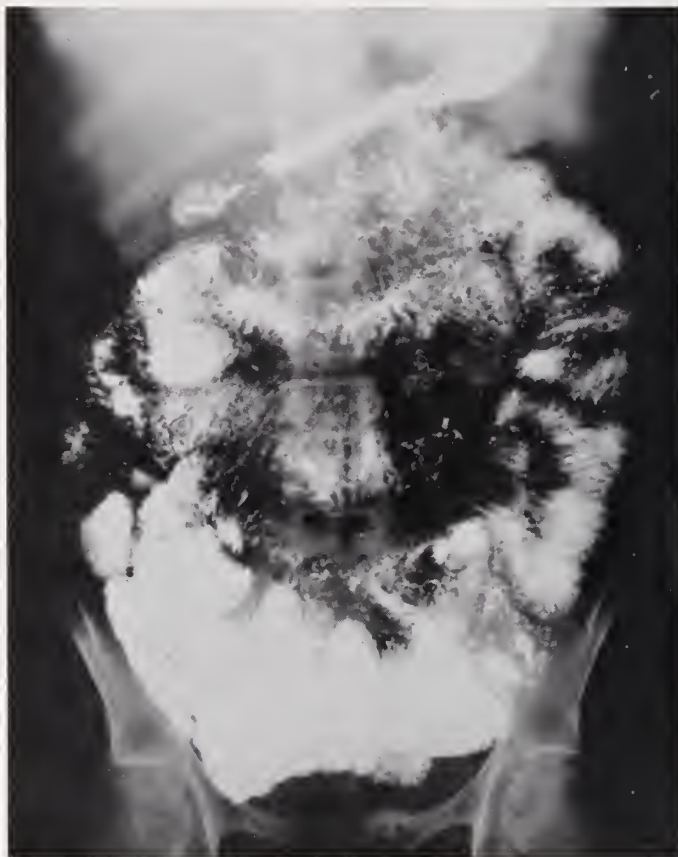


FIG. 2 Dilatation of loops of small intestine with marked coarsening of mucosal folds and increased secretions. A later film demonstrated more prominent segmentation and flocculation of the barium.

a low fat, high protein diet and parenteral crude liver extract, folic acid, vitamin B<sub>12</sub>, and hexavitamins. She responded well to this regimen with disappearance of her diarrhea and edema prior to her discharge on September 10, 1957. When last heard from, 15 months later, she was completely asymptomatic on a gluten-free diet.

#### DISCUSSION

The presence of marked hypogammaglobulinemia was unequivocally established in this patient by the results of electrophoresis and the zinc sulfate turbid-

ity test. Splenomegaly, which is a frequent finding in acquired hypogammaglobulinemia, was present but decreased lymphocytes in the peripheral blood, which is also common, was not present. Striking by its absence was the usual history in hypogammaglobulinemia of multiple recurrent infections. In this regard she resembles the patient described by Malvezin *et al.* who also presented as a case of malabsorption syndrome clinically, without an unusual history of

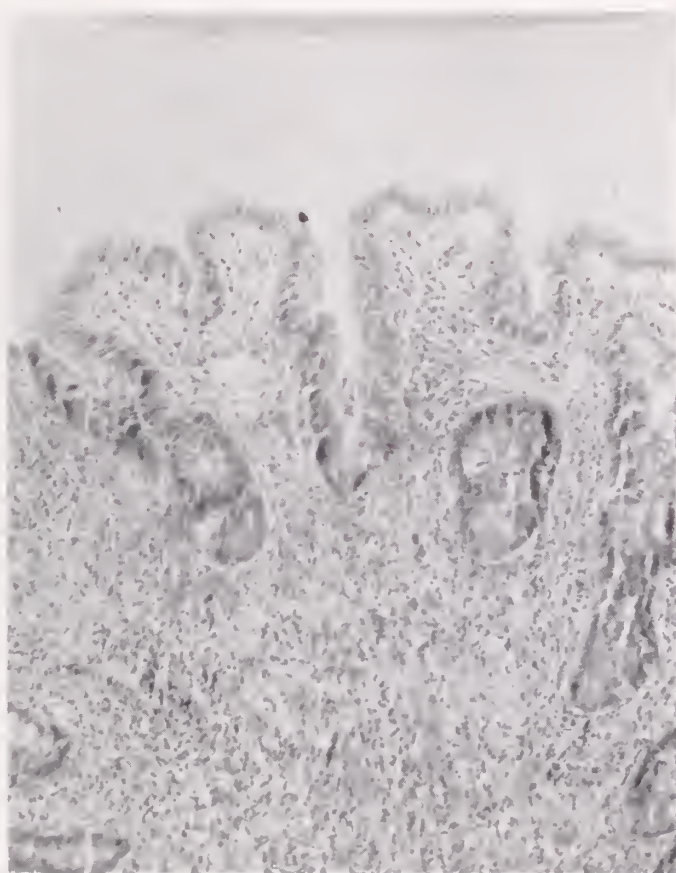


FIG. 3. Jejunal mucosal biopsy with flattening and atrophy of the mucosa, marked diminution of the absorbing surface, and increased cellularity. (Hematoxylin and eosin  $\times 125$ )

infections (18). The reasons for the absence of such a history in these cases is not clear.

Although her parasitic infestation complicates the evaluation of her history of diarrhea, the results of her absorption studies, small bowel x-rays, serum lipids, and especially her jejunal mucosal biopsy substantiate the diagnosis of primary malabsorption syndrome. The normal fecal fat excretion, although unusual, was determined during a period of complete clinical remission. The features of her case are such that we do not feel justified in categorizing her as either

tropical or nontropical sprue. We would prefer to consider her as a case of primary malabsorption syndrome, without a more specific designation.

The relationship between hypogammaglobulinemia and sprue is not clear. There are many causes of diarrhea in patients with acquired hypogammaglobulinemia, as previously noted, and the incidence of sprue in these patients will only be determined when the individual cases of diarrhea are thoroughly investigated. However, the six previously reported cases of probable sprue plus the present case in a disease as relatively rare as acquired hypogammaglobulinemia would indicate that the incidence of sprue in these patients is probably elevated. It is unlikely that the marked hypogammaglobulinemia in these patients with normal total serum proteins is secondary to the sprue. In sprue a low gamma



FIG. 4. Jejunal mucosal biopsy with a lesser degree of atrophy. The preserved villi are clubbed at their tips and many are in the process of fusion. (Hematoxylin and eosin  $\times 44$ )

globulin is ordinarily found only in conjunction with a generalized lowering of all the serum proteins, and loss of gamma globulin alone into the gut has not been reported. If the sprue were secondary to the hypogammaglobulinemia and a resultant alteration in antibody mechanisms, it would seem probable to find an increased incidence of sprue in the congenital form of the disease, but this apparently does not occur. Other explanations for the association include the possibilities that the acquired hypogammaglobulinemia and the sprue are both expressions of some unknown underlying disease process or that they are both somehow connected genetically. At the present time there is insufficient information available to determine the mechanism of the association.

#### SUMMARY

A) A patient with acquired hypogammaglobulinemia and clinical, laboratory, and histological evidence of sprue is presented.

B) Although there are multiple causes to explain the high incidence of diar-

rhea in patients with acquired hypogammaglobulinemia, there appears to be an increased incidence of the primary malabsorption syndrome in these patients.

C) Possible explanations for the association are discussed.

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## NEEDLE BIOPSY OF BONE MARROW

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In 1958, McFarland and Dameshek reviewed the methods which have been used to obtain fragments of bone marrow for histologic study and proposed a new technique of posterior iliac crest biopsy utilizing the Vim-Silverman needle (1). The advantages of this simple, efficient and easily mastered technique are several: 1. a relatively large fragment of bone marrow is obtained without excessive artifactual alteration; 2. the procedure can be undertaken without prior preparation whenever a "Dry Tap" is encountered on routine marrow aspiration; 3. an open surgical biopsy is usually precluded; 4. adequate hematologic smears are frequently obtained during the biopsy procedure; 5. the method can be utilized to serve other purposes *e.g.* biopsy of bone tumors.

### METHOD

The manipulative procedure used is as outlined by McFarland and Dameshek with slight modification (1). The patient is placed in the knee-chest position on his side as for lumbar puncture. The posterior iliac crest is palpated and followed posteriorly to the posterior superior iliac spine. The iliac dimples serve as landmarks in thin individuals. A thumbnail imprint is made on the skin over the posterior superior iliac spine for future reference. The skin is prepared with an antiseptic solution and the field is draped with sterile towels. Procaine is injected locally, with care to completely infiltrate the periosteum of the posterior superior iliac spine.

A standard Vim-Silverman needle is introduced down to the most prominent point of the posterior superior iliac spine. At this time, it is beneficial to "walk" the tip of the needle over the surface of the spine so that its medial and lateral margins are delimited. The needle is then placed at the midpoint of the width of the spine and positioned so that it parallels the upper border of the posterior iliac crest. When in the proper position, it will be angled slightly laterally and cephalad from the point of entry. The tip of the needle should now rest on the most prominent portion of the posterior superior iliac spine.

With a slight rotatory motion, the needle with the stylet in place is advanced through the cortex, which is very soft in this area. A slight "give" is felt as the marrow space is entered. After the marrow is entered, the stylet is removed and strong suction is applied with a 20 cc syringe. Frequently, adequate material may be aspirated with which the usual type of bone marrow smear may be made. Following the aspiration, the cutting blades of the Vim-Silverman needle are introduced. While steadying the outer needle, the cutting blades are pushed

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straight forward. They are introduced approximately 1.0 to 1.5 cm. During this procedure, a grating sensation is felt as bony trabeculae are broken. When the cutting blades have been introduced to the desired depth, the hub of the blades is held firmly in position and the outer needle is rotated and advanced approximately 0.5 to 1.0 cm. If any resistance is met, the outer needle is not advanced further. The hubs of both the outer needle and the cutting blades are then grasped firmly and together are rotated  $\frac{1}{8}$  of a turn and simultaneously withdrawn.

Upon removal of the needle the bone marrow core is seen to be clasped between the cutting blades. Since the blades are usually slightly spread apart by the bony core, they cannot be withdrawn through the needle. Therefore, the cutting blades are advanced all the way so that the tips project from the outer needle. A small hypodermic needle is used to separate the cutting blades, by forcing the point between the blades where they emerge from the outer needle. The bony core may now be easily displaced with the stylet of the Vim-Silverman needle. The core is either fixed immediately in 10% neutral buffered formalin or used to make touch preparations prior to fixation. If touch preparations are made, care must be taken not to crush the bone core. After the bone core is dislodged, the blades of the Vim-Silverman needle are withdrawn and spread apart. If any marrow aggregates are identified, smears are prepared for routine examination. The bone core is then fixed for 12 to 24 hours, decalcified for 6 to 12 hours and subjected to routine histopathologic examination.

After the biopsy is completed, pressure is applied to the skin at the point of entry of the needle for 1 to 3 minutes, after which bleeding ceases. A small compress is taped into position and is removed in 12 hours. The patient experiences no more discomfort than is associated with a routine bone marrow puncture, and no special precautions are needed.

Occasionally difficulty may be encountered in advancing the cutting blades of the Vim-Silverman needle. This is most often due to the needle not being placed in the center of the marrow space of the posterior iliac crest, so that it abuts on the medial or lateral cortical walls. If this occurs, the needle should be repositioned so that it parallels the lateral and medial walls of the posterior iliac crest. No failures to obtain bone have been encountered if the needle was properly placed.

In addition to the posterior iliac crest, biopsies have been obtained from the anterior iliac crest and isolated tumors of the ilium and humerus.

#### RESULTS

This method has been used in all cases of failure to obtain adequate marrow by the usual means ("Dry Taps"), in selected cases of primary or metastatic malignancy of the bone and in suspected cases of miliary tuberculosis and sarcoidosis.

The bone marrow biopsy has yielded a definitive diagnosis in 22 of 31 cases (71%) (Table I). These have included many diversified indications. If the biopsies are limited to those cases yielding a "Dry Tap," diagnoses have been obtained on 15 of 15 biopsies (100%). When prior aspiration has yielded adequate

TABLE I

Case	Clinical Diagnosis	Pathological Diagnosis
O.R.	Schistosomiasis with secondary hypersplenism.	Hypercellular marrow with marked increase of eosinophils
A.J.	Post Thio-TEPA aplastic anemia.	Aplastic marrow.
J.B.	Sarcoidosis	Normal
R.G.	Leukemoid reaction, etiology undetermined.	Miliary tuberculosis
E.M.	"Dry Tap" (patient known to have leukemic reticuloendotheliosis).	Leukemic reticuloendotheliosis
H.R.	"Dry Tap" (patient had a leukoerythroblastic anemia).	Myelofibrosis
B.G.	"Dry Tap" (patient had carcinoma of the prostate)	Metastatic carcinoma
S.G.	"Dry Tap" (patient had pancytopenia)	Acute leukemia
S.G.	"Dry Tap" (patient had refractory anemia)	Hypoplastic bone marrow
W.P.	"Dry Tap" (patient had lymphosarcoma with a leukoerythroblastic anemia)	Fibrosis of marrow space
A.G.	"Dry Tap" (patient had myeloid metaplasia)	Myelofibrosis
E.W.	Paraplegia	Metastatic carcinoma
L.J.	"Dry Tap" (patient had long exposure to benzol)	Fibrosis of marrow space
C.R.	Sarcoidosis	Normal
J.MCB.	Lymphoma	Metastatic carcinoma
S.G.	Metastatic carcinoma	Normal
P.R.	"Dry Tap" (patient had "spent" polycythemia vera)	Myelofibrosis
I.F.	"Dry Tap" (patient had enlarged spleen and marked "shift to the left")	Chronic myelogenous leukemia
M.H.	Lymphoma	Normal
O.L.	Possible tuberculosis	Normal
Y.G.	Wegener's granulomatosis	Normal
A.K.	"Dry Tap" (patient had enlarged spleen and leukoerythroblastic anemia)	Chronic myelogenous leukemia
L.W.	Metastatic carcinoma	Metastatic carcinoma
I.S.	Hypersplenism	Sarcoidosis
I.O.	Hyperparathyroidism	Marrow fibrosis compatible with hyperparathyroidism
G.R.	"Dry Tap" (patient had myelofibrosis)	Myelofibrosis
N.K.	"Dry Tap" (patient had myeloid metaplasia)	Myelofibrosis
S.O.	"Dry Tap" (patient had refractory anemia)	Hypoplastic marrow
A.F.	"Dry Tap" (patient had pancytopenia and hepatosplenomegaly)	Leukemic reticuloendotheliosis
J.A.	Gaucher's disease	Gaucher's disease
A.R.	Miliary tuberculosis	Normal

marrow, only 10 of 16 biopsies (63%) have yielded a positive diagnosis. Therefore, it is clear that this method has its greatest value in cases where a "Dry Tap" is obtained.

The diagnoses made in this series (Table I) have included myelofibrosis (Fig.

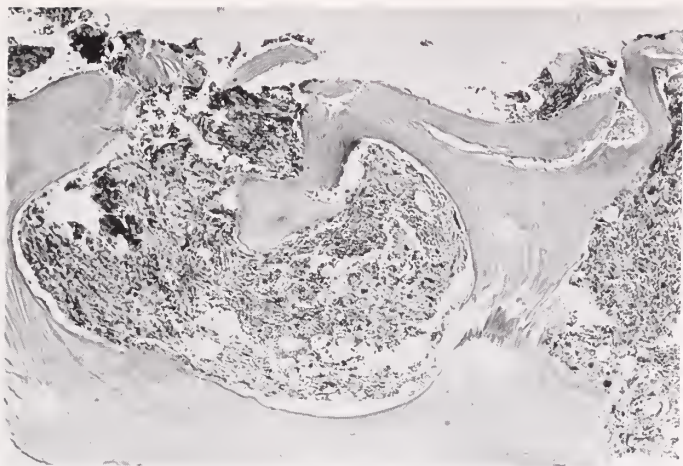


FIG. 1. Myelofibrosis showing increase of megakaryocytes and fibrosis. (H & E  $\times 40$ )

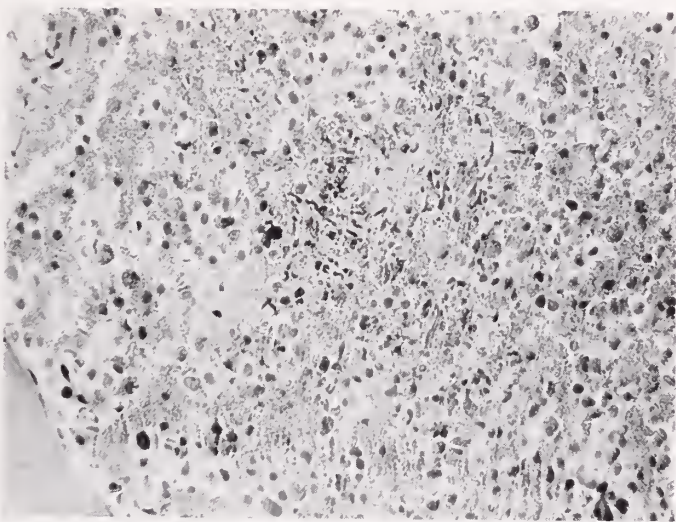


FIG. 2. Chronic myelogenous leukemia with marked prominence of eosinophils. (H & E  $\times 100$ )



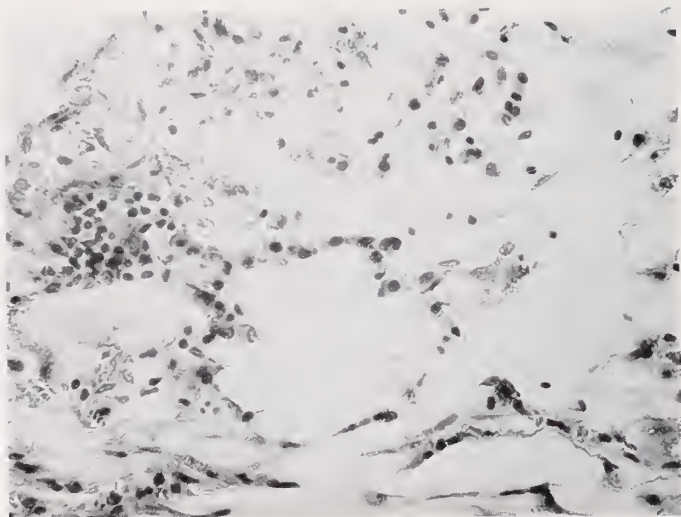


FIG. 3. Post Thio-TEPA aplasia with empty marrow space and prominent plasma cells. (H & E  $\times 150$ )

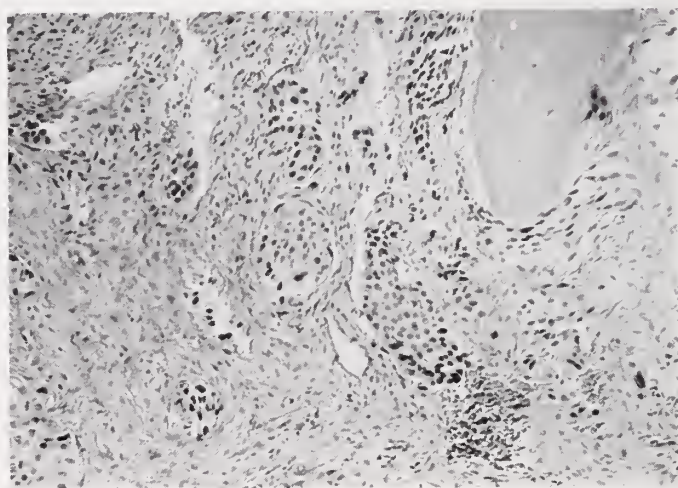


FIG. 4. Metastatic squamous cell carcinoma. (H & E  $\times 100$ )

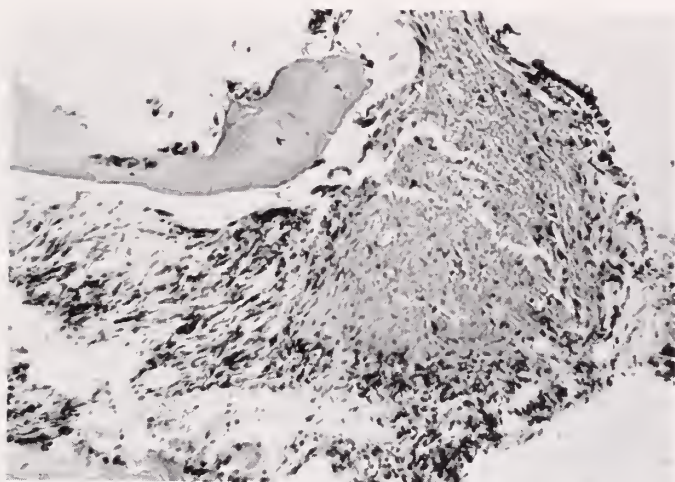


FIG. 5. Miliary tuberculosis showing caseating granuloma positive for acid fast bacilli. (H & E  $\times 100$ )

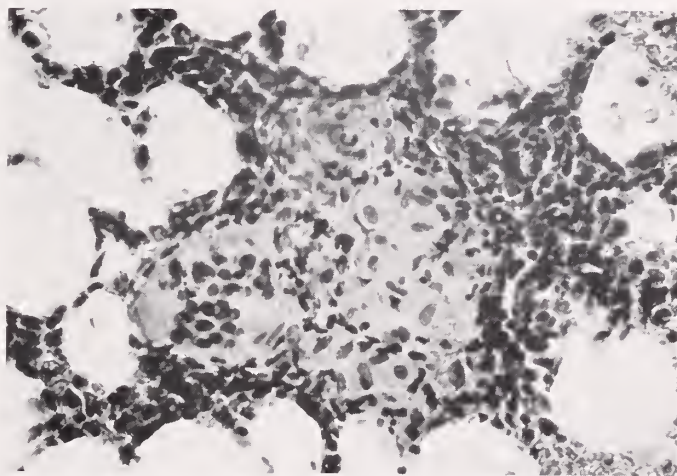


FIG. 6. Sarcoidosis showing noncaseating granuloma with epithelioid and giant cells. (H & E  $\times 400$ )

1), chronic myelogenous leukemia (Fig. 2), acute leukemia, leukemic reticulo-endotheliosis, aplastic anemia (Fig. 3), hypoplastic bone marrow, metastatic carcinoma (Fig. 4), hyperparathyroidism, miliary tuberculosis (Fig. 5) and sarcoidosis (Fig. 6).

The diagnoses obtained on biopsy have most often obviated the need for more extensive diagnostic procedures, such as open surgical biopsy, or have proved definitive when other methods have failed. Indeed, since this method has been in use only one open biopsy has been performed to confirm a needle biopsy diagnosis of hypoplastic marrow.

Therefore, it is felt that this method should be added to the routine hematologic procedures and should replace open biopsy as a primary diagnostic procedure.

#### SUMMARY

A method of performing a Vim-Silverman bone marrow biopsy is presented and experience gained with this technique is reviewed.

Its efficacy in evaluating hematologic, neoplastic and inflammatory processes of bone is stressed.

#### REFERENCE

1. McFarland, W., and Dameshek, W.: Biopsy of Bone Marrow with the Vim-Silverman Needle. *J.A.M.A.*, 166: 1464, 1958.

# THE EFFECT OF URINE HYDROLYSIS ON NUCLEOPROTEINS IN NORMAL, LEUKEMOID AND LEUKEMIC LEUKOCYTES

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The diagnosis of certain types of leukemias has been limited on occasion by the difficulty in recognizing malignant hemopoietic tissue, despite recent advances in morphological and biochemical criteria. Since enzymatic nucleoprotein hydrolysis has been an aid in cellular identification, the application of this technique was studied in the differentiation of normal, reactive and leukemic blood.

## METHOD

The method of enzymatic nucleoprotein hydrolysis used in this study was based on a modification of Laves' technique for urine hydrolysis of white blood cells (1); peripheral blood smears were fixed in methyl alcohol for two minutes, with freshly voided urine serving as the source for nuclear hydrolysis. This technique was modified by flooding the fixed smears with urine and gently steaming them for five minutes; after ten minutes without further heating the slides were rinsed in water and stained with fresh Giemsa stain for fifteen minutes. Two additional slides were made simultaneously for each subject, with tap water used instead of urine on one, and urine that had been boiled for five minutes and cooled to room temperature used on the second. The steaming and the staining of the slides were identical with the procedures previously described.

Subjects studied included those with normal blood smears, leukemoid reaction, acute monocytic leukemia, acute and chronic lymphatic leukemia, acute and chronic myelogenous leukemia, erythroleukemia and myeloid metaplasia. The majority of the patients were not receiving antileukemic therapy during the study.

## RESULTS

### *Water-Giemsa Stain*

With this stain the nuclear and cytoplasmic morphological characteristics of the white blood cells of the normal subjects were readily apparent and were, in fact, similar to those seen in the conventional Jenner-Giemsa or Wright stain (Table 1).

The characteristic nuclear structure of the immature and the mature myeloid cells in the subjects with the leukemoid reaction, acute and chronic myelogenous leukemia, were apparent. The fine nuclear chromatin pattern of the abnormal monocytes in the subjects with acute monocytic leukemia was noted as was the

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TABLE I

*Summary of Results of Urine Hydrolysis of Normal, Leukemoid and Leukemic Blood Smears*

Blood Smears from:	Number Studied	Morphologic Descriptions									Comments
		Nuclear Blanching			Nuclear Chromatin Pattern			Cytoplasmic Granules			
		H <sub>2</sub> O	Fresh Urine	Boiled Urine	H <sub>2</sub> O	Fresh Urine	Boiled Urine	H <sub>2</sub> O	Fresh Urine	Boiled Urine	
Normal	6										
granulocyte		0	0	0	N	C/A	N/C	+	0	0	
lymphocyte		0	0	0	N	N/C	N/C	—	—	—	
monocyte		0	0	0	N	N/A	N	+	0	0	
eosinophil		0	0	0	N	N	N	+	+	+	
Leukemoid*	3	0	+	0	N	C/A	N/C	+	0	0	Eosinophil, lymphocyte monocyte as in normal
Acute Myelogenous leukemia*	4	0	0	0	N	C/A	N/C	+	0	0	“ “
Chronic Myelogenous leukemia*	12	0	++++	0	N	C/A	N/C	+	0	0	“ “
Myeloid metaplasia*	8	0	0	0	N	C/A	N/C	+	0	0	“ “
Erythroleukemia*	2	0	0	0	N	C/A	N/C	+	0	0	“ “
Acute Lymphatic leukemia**	2	0	0	0	N	occ. C	N/C	—	—	—	Eosinophil, monocyte, granulocyte as in normal
Chronic Lymphatic leukemia**	8	0	0	0	N	occ. C	N/C	—	—	—	“ “
Acute Monocytic leukemia***	2	0	0	0	N	A	N/C	+	0	0	Eosinophil, lymphocyte, granulocyte as in normal

\* Description of myelocytic cells only.

\*\* Description of lymphocytic cells only.

\*\*\* Description of monocytic cells only.

N: Normal.

A: Absent.

C: Clumped.

nuclear structure of the lymphocytic cells in the subjects with acute and chronic lymphocytic leukemia.

#### *Fresh Urine-Giemsa Stain*

Under this stain the morphological characteristics of the white blood cells of the normal subjects could still be recognized. However, when the urine slide was compared with the water slide, differences in the nuclei and the cytoplasm were noted. The azurophilic cytoplasmic granulation in the myelocytic and monocytic cells had disappeared and the cytoplasm appeared grey and homogeneous. Eosinophilic granules of the eosinophils were still present. In the myelocytic cells the nuclear chromatin pattern appeared either coarsely clumped or completely absent. When the chromatin was absent the nuclei appeared smooth and uniform. Clumping of nuclear chromatin was occasionally seen in the lymphocytes. There appeared to be no change in the nuclei of the eosinophils or monocytes.

The most striking finding noted in the fresh urine stain was in the myelocytic nuclei of subjects with chronic myelogenous leukemia (Fig. 1). The nuclei of many cells, from myeloblast to polymorphonuclear neutrophil, showed nuclear blanching, *i.e.*, failure of the nucleus to take the Giemsa stain. This effect was more pronounced in the early myelocytic cells. However, nuclear blanching was not a uniform finding, for in the same microscopic field, cells of similar maturity were seen with normal appearing nuclei, "ghost nuclei" and partially blanched nuclei.

Nuclear blanching of the myelocytic cells was not observed in subjects with normal blood smears, myeloid metaplasia, erythroleukemia, acute monocytic leukemia, acute and chronic lymphocytic leukemia, and, interestingly, in acute myeloblastic leukemia.

The nuclei of the myelocytic cells in the subject with leukemoid reaction showed slight blanching, again more prominent in the earlier cells (Fig. 2). None of the nuclei in these cells were completely blanched.

In the subject with acute monocytic leukemia the fine nuclear chromatin pattern of the abnormal monocytes was lost and the nuclei appeared homogeneous. Clumping of nuclear chromatin was occasionally seen in the leukemic lymphocytes.

Contrary to the findings in the normal subject, the azurophilic cytoplasmic granulation in the myelocytic and monocytic cells in the leukemoid and leukemic subjects was not seen.

#### *Boiled Urine-Giemsa Stain*

Under this stain it was also possible to identify all the white blood cells. There were two major differences between this stain and the fresh urine stain. There was no nuclear blanching whatsoever in the myelocytic cells in subjects with chronic myelogenous leukemia or leukemoid reaction and there was no loss of nuclear chromatin in normal myelocytic cells. The boiled urine stain was similar to the fresh urine stain in two respects. There were no azurophilic granules in the

cytoplasm of the myeloid and monocytic cells and the nuclear chromatin of many of the white cells appeared coarsely clumped.

#### DISCUSSION

Brachet demonstrated that if a cell was incubated in a solution of ribonuclease, its cytoplasmic granules would lose their pyrimphilia (2). Using Brachet's technique, Laves and Thoma demonstrated that if neutrophilic granulocytes were incubated in a solution of ribonuclease the nuclei would lose their basophilia, *i.e.*, fail to take the Giemsa stain (3). They observed that after prolonged hydrolysis the nuclei became vacuolated, leaving only a fine Feulgen-positive structure. Even after prolonged hydrolysis in ribonuclease the nuclei of the eosinophils, monocytes, and lymphocytes remained intact. An opposite

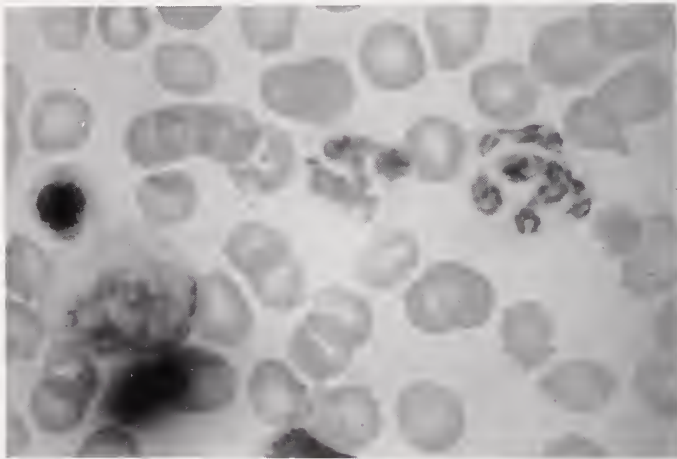


Fig. 1. Effect of urine nucleoprotein hydrolysis in chronic myelogenous leukemia; a. Water-Giemsa stain: absence of nucleoprotein hydrolysis in a promyelocyte, two polymorphonuclear neutrophils and normoblast.

effect occurred with desoxyribonuclease. The nuclear chromatin of the eosinophil, monocyte, and lymphocyte completely lost their basophilia. However, the nuclear structure of the neutrophilic granulocytes was only somewhat reduced by the desoxyribonuclease.

Laves obtained the same results with neutrophilic granulocytes when urine was used as a source of ribonuclease (1). Aleksandrowicz and Perkowska were also able to hydrolyze the nuclei of human granulocytes by exposing them to the action of urinary dialysates, saliva, and crystalline ribonuclease (4). Sprague, working with Laves' method, initially concluded that the nuclear protein of the granulocyte was largely ribonucleoprotein whereas it was desoxyribonuclease protein in the mononuclear cells and in the eosinophil (5). He found no difference between the reactions of normal and leukemic cells.

Gardner, Wright and Williams successfully employed the urine hydrolysis test to differentiate myelocytic cells from other leukocytes (6). Lysing the nuclei of the myelocytic cells was best achieved with neutral or slightly alkaline urine at a temperature of 60°C for fifteen minutes. Only a solution of desoxy-

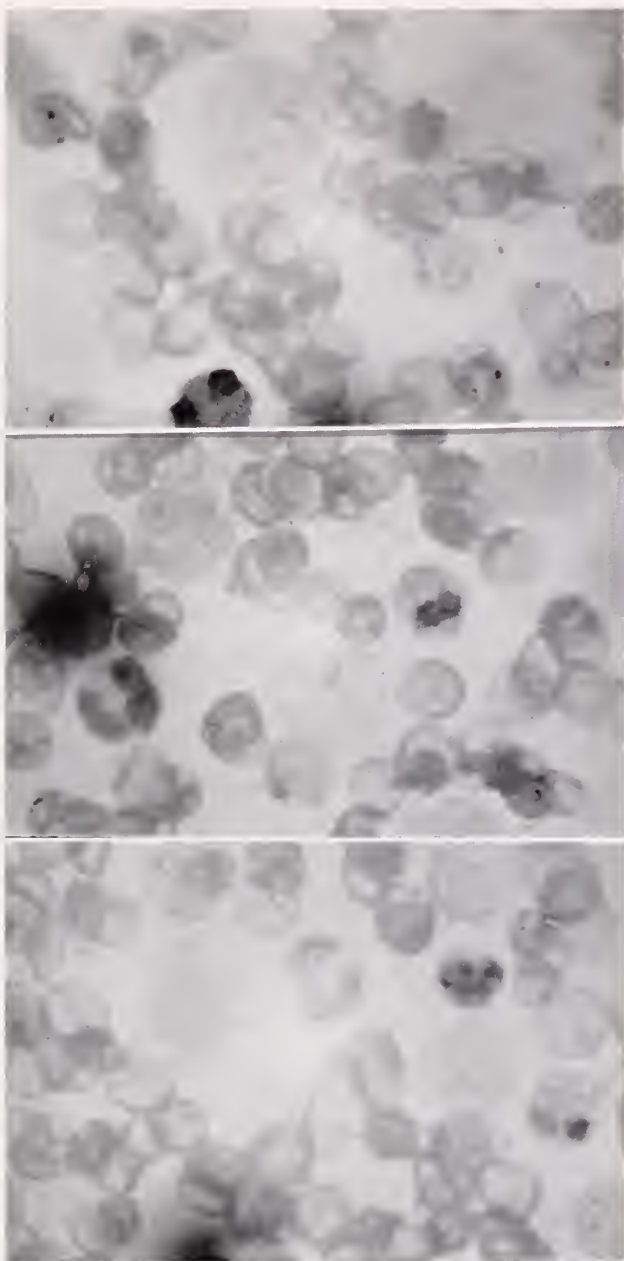


FIG. 1b. Fresh urine-Giemsa stain: three photographs illustrating nucleoprotein hydrolysis in mature and immature myelocytic cells; note absence of nuclear blanching in the eosinophil and nonsegmented neutrophil and partial nuclear blanching occurring in two polymorphonuclear neutrophils.



ribonuclease in buffered saline produced effects comparable to those achieved with urine. Purified ribonuclease, desoxyribonuclease and various concentrations of sodium chloride did not produce a comparable effect. These authors claimed that the test was valid in 17 of 18 cases of leukemia.

We observed complete nuclear blanching only in the myelocytic cells of subjects with chronic myelocytic leukemia. No nuclear blanching occurred in myeloid cells in subjects with acute myelogenous leukemia. Gardner, Wright and Williams also noted similar results in four subjects with chronic myelocytic leukemia. In acute myelogenous leukemia they observed polymorphonuclear blanching in three subjects. Interestingly enough, in two of three of these subjects they did not observe nuclear blanching in the immature myelocytic cells. The marked difference in the reaction between the acute and chronic form of

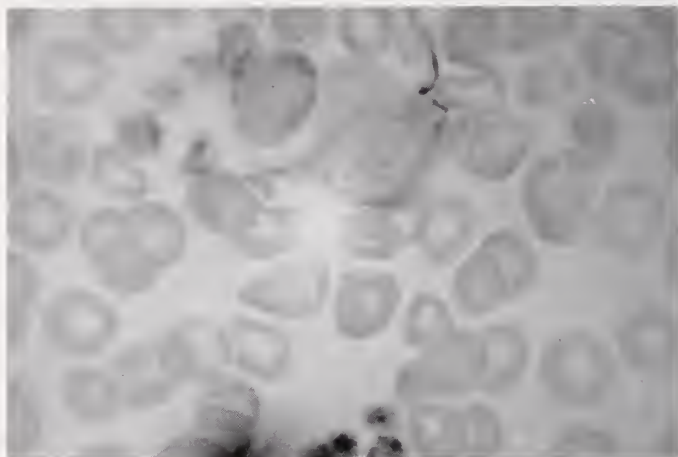


Fig. 1c. Boiled urine-Giemsa stain; loss of nuclear detail without definite nuclear blanching in both mature and immature myelocytic cells (note loss of cytoplasmic granulation in b and c).

myelogenous leukemia suggested to us the possibility of a cytochemical difference between the two diseases.

Biochemical differences between the acute and the chronic forms of myelogenous leukemia have been demonstrated previously. The leukocyte alkaline phosphatase activity is low to absent in chronic myelogenous leukemia and normal to reduced in the acute disease. Aleksandrowicz and his co-workers have reported a consistent relationship between the low serum and increased urinary ribonuclease content in subjects with chronic myelogenous leukemia (8). They did not observe this relationship in subjects with acute myelogenous leukemia or in other leukemias under study.

We found that fresh urine produced a greater degree of nuclear blanching in the earlier myelocytic cells of the subjects with chronic myelocytic leukemia and those with leukemoid reaction. Perkowska found that the nuclear chromatin of immature cells of the myelocytic series was more susceptible to hydrolysis by a urine dialysate than were the older cells (9).

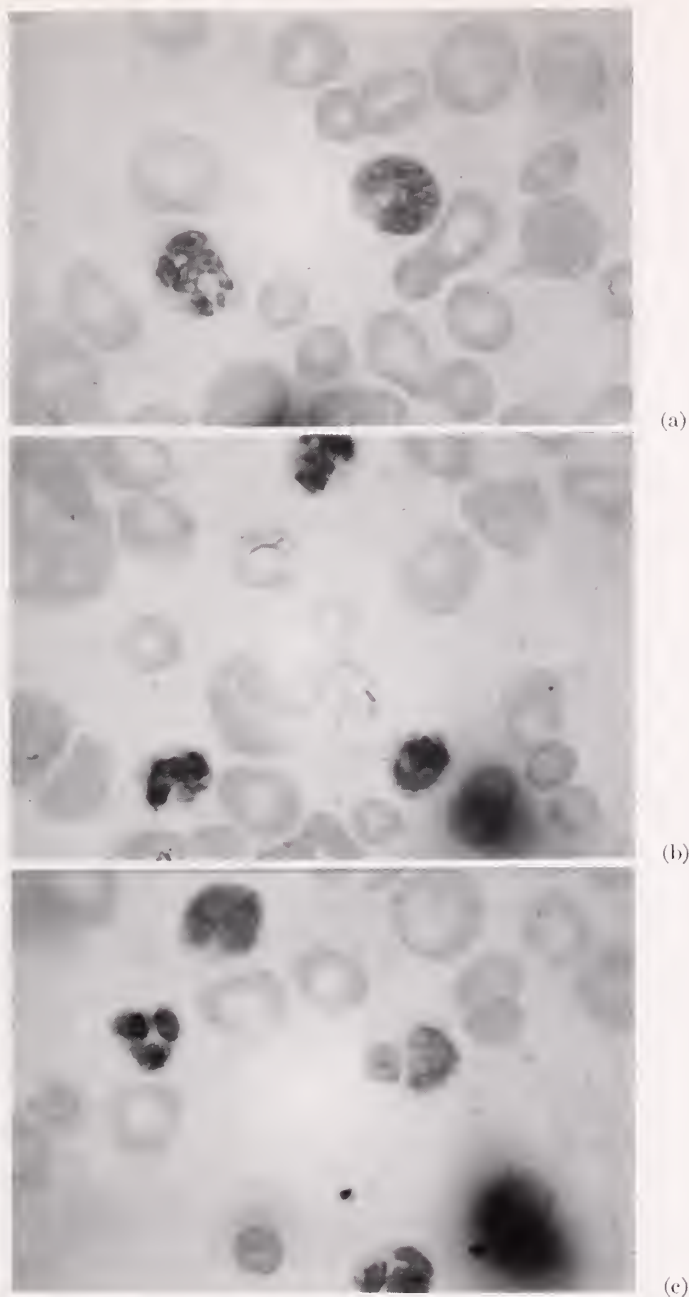


FIG. 2. Effect of urine nucleoprotein hydrolysis in a leukemoid reaction: a. Water-Giemsa stain: preservation of nuclear detail in a polymorphonuclear neutrophil and metamyelocyte; b. Fresh urine-Giemsa stain: coarse clumping of nuclear chromatin and loss of cytoplasmic granulation in three myelocytic cells; c. Boiled urine-Giemsa stain: chromatin clumping and loss of nuclear detail without nuclear blanching in several myelocytic cells.

Thorell's techniques of nucleoprotein analysis also showed that white blood cells of leukemia subjects differed from comparable cells in normal subjects (10). He noted that the marked reduction in ribose polynucleotide in normal maturing white blood cells did not occur in leukemic cells. The latter cells also contained a much higher concentration of ribose polynucleotide in their cytoplasm and nucleoli than normal cells of comparable maturity. Thorell also believed that the differences he found in cell maturation would make possible a measurable distinction between normal and pathological courses of blood formation.

Although urine is known to contain ribonuclease, knowledge of the nucleoprotein composition of human cells would make it unlikely that one could attribute the phenomenon of nuclear blanching in myelocytic cells to ribonuclease activity. Additional studies by Sprague led him to modify his earlier impressions of the effect of urine on granulocytes (11). He found the hydrolytic activity of urine was lost when the urine was dialyzed against distilled water but not when it was dialyzed against tap water. The activity of the urine was slightly diminished when its pH was alkaline and greatly diminished when heated for thirty minutes. Sprague obtained similar effects of nuclear blanching with certain concentrations of sodium chloride and buffered phosphate solutions but not with commercial ribonuclease.

On the basis of his later studies Sprague suggested that urine may act as a salt solution to extract nucleoprotein. Yet he still admitted there was an additional possibility that this extraction was due to some proteolytic enzymatic activity in urine. He accounted for the nuclear blanching of the granulocytes (as opposed to the lack of blanching in the monocytic cells) to a difference in binding between the nuclei acid and the basic protein of the two cell types.

Evidence was found for and against urine enzymatic activity on white cell nuclei and cytoplasm, *viz.*, a complete blanching of myelocytic cells in subjects with chronic myelogenous leukemia and faint blanching in subjects with leukemoid reaction. There was loss of nuclear chromatin pattern in the monocytic and myelocytic cells on slides incubated in fresh urine. When the urine was boiled these effects were not observed. This suggested a heat-labile factor in the urine. Evidence against enzymatic activity in urine included the loss of azurophilic cytoplasmic granulation in the myelocytic and monocytic cells in slides of both fresh and boiled urine. Also the coarse clumping of nuclear chromatin was seen in slides with both fresh and boiled urine. These effects must be attributed to a heat-stable factor in the urine.

The failure of nuclei to take the Giemsa stain following application of urine, desoxyribonuclease in buffered saline or ribonuclease, has been reported (1, 3-6, 11). Although "enzymatic hydrolysis" has been considered to be a factor, the precise mechanism still remains obscure.

In our study fresh urine also produced variations in nuclear blanching among myelocytic cells of subjects with chronic myelogenous leukemia. These variations, if not technical, suggested the possibility that cytochemical differences may exist between leukemic cells or that "normal" and "abnormal" cells may coexist in leukemia. The faint nuclear blanching noted in the leukemoid reac-

tion may indicate some relationship between the normal leukocytosis reaction and the leukemic state of chronic myelogenous leukemia.

#### SUMMARY

The occasional difficulty in recognizing malignant hemopoietic tissue led us to use a technique of nucleoprotein hydrolysis in an attempt to differentiate normal, reactive and neoplastic blood cells. Freshly voided urine was used as the source for nucleoprotein hydrolysis, with controls of water and boiled urine. The subjects studied included normals, leukemoid reaction, myeloid metaplasia and a variety of leukemias.

Complete nuclear blanching, *i.e.*, failure of the nuclei to take the Giemsa stain, was observed only in the cells of subjects with chronic myelogenous leukemia, the effect being more pronounced in the younger cells. Faint nuclear blanching was noted in the myelocytic cells of the subjects with leukemoid reaction. There was no nuclear blanching whatsoever in the subjects with normal blood, acute myeloblastic leukemia, myeloid metaplasia and other leukemias studied.

This study provides evidence for both an enzymatic and a nonenzymatic factor(s) in urine responsible for nucleoprotein hydrolysis.

Our observations further confirm previous reports of cytochemical differences between acute and chronic myelogenous leukemia.

#### ACKNOWLEDGMENT

The author wishes to thank Dr. Louis Wasserman for his helpful suggestions in the preparation of this manuscript.

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## URETERAL FISTULA FOLLOWING SURGERY FOR INFLAMMATORY RETROCECAL MASS

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Injury to the middle third of the ureter during intra-abdominal surgery is most uncommon. All previously reported instances of this complication involved the right ureter and occurred when operative procedures were performed in the presence of a retrocecal mass secondary either to appendicitis, perforated cecal carcinoma or nonspecific inflammation (1, 2). As in the case reported herein, the inflammatory process, by displacing and fixing the right ureter, greatly increased the hazard of its accidental clamping and/or transection.

M.S. (№80427), a 14½ year old white youth had been in normal health until November, 1956, when he developed a chronic cough and was noted to have a leukocytosis of 20,000 with a 9% eosinophilia. There was malaise, and a low grade intermittent fever. Subsequently, after a three day period of lower right quadrant pain and diarrhea, he was admitted to a hospital in Washington, D. C. on December 18, with a diagnosis of appendicitis. Laboratory studies showed the white blood cell count to be 20,700/mm<sup>3</sup> with 87% neutrophils and 13% lymphocytes. Sedimentation rate was 27 mm per hour (normal 18 mm). Urinalysis was negative. Agglutination reactions were negative for typhoid, undulant fever and tularemia. Laparotomy was performed. A three inch wide retrocecal mass was noted, which was firm and which pushed the cecum and adjacent iliocecal mesentery anteriorly. The overlying peritoneum was hyperemic and there was a slight thickening and hyperemia of the appendix. The gross findings were insufficient to confirm the diagnosis of appendicitis. Appendectomy was performed and then the peritoneum lateral to the cecum was incised and several pieces of tissue were removed for biopsy. These were reported as showing "chronic inflammatory tissue." Some difficulty was encountered in controlling the bleeding of the biopsied areas. The abdomen was closed without drainage. The postoperative course was stormy. On January 1, 1957, fluctuation of the wound was noted and aspiration yielded 15 cc of pus. The white blood cell count was 41,000/mm<sup>3</sup> at this time with 91% polymorphonuclear leukocytes and a marked shift to the left.

On January 2, 1957, the patient was examined by one of us in consultation (J.J.L.). He was found to be acutely ill with a temperature of 101°F. The abdomen was distended. Situated on the right side, subjacent to the operative wound was a six inch in diameter, tender, indurated mass, which drained a yellow-brown purulent material. There was x-ray evidence of paralytic ileus. Exploration of the wound and drainage of the mass was advised. Several ounces of cloudy, serous fluid were evacuated and a tube drain inserted. The situation improved and the patient was able to leave the hospital. On January 16, 1957, the wound

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edges separated and there was copious drainage of cloudy serous material. The wound remained opened and continued to drain a pint of straw-colored fluid a day, which at times was noted to have an ammoniacal odor. During the next six weeks, while the wound was gradually granulating, drainage continued and the patient had recurrent bouts of fever associated with wound pain and diar-



FIG. 1. Preoperative barium enema demonstrating a retrocecal mass elevating and displacing the cecum medially. No intrinsic disease of the cecum and ileum is evident.

rhea. Barium enema and G.I. studies showed a right lower quadrant mass displacing the distal ileum and cecum medially upward and anteriorly (Fig. 1).

The patient was brought to New York at this time. The wound was probed and a yellowish, watery discharge, urinous in character, was observed. A long tube drain was inserted into the wound. Intravenous pyelography was then performed, which showed a normal left kidney and marked dilatation of the right renal pelvis and of the upper two-thirds of the right ureter. The lower third of the right ureter could not be seen. The patient was admitted to The Mount Sinai

Hospital on March 22, 1957. Barium enema was repeated and this showed the mass in the right lower quadrant to have diminished in size. No evidence of intrinsic abnormality in the right side of the colon or ileum was noted. The right kidney was incompletely and very faintly delineated by intravenous ur-



FIG. 2. Preoperative intravenous urogram showing faint visualization of markedly dilated calices of the right kidney. The left kidney, ureter and bladder are normal.

ography (Fig. 2). The calyces were markedly dilated. The right ureter could not be identified. Cystoscopic examination showed the bladder to be normal. A #5 catheter was passed 10 cm up the right ureter, where it was obstructed. Bulb pyelography demonstrated the lower 10 cm of the right ureter to be of normal calibre. Above this level there was an abrupt transition to a markedly dilated ureter with considerable tortuosity (Fig. 3).

## COURSE

It was evident from the clinical course and the urologic findings that the middle third of the right ureter had been injured during the original surgical procedure and that marked stenosis and a uretero-cutaneous fistula had resulted. Progressive deterioration of the right kidney was taking place. Urinary



FIG. 3. Preoperative retrograde bulb pyelogram delineates the normal lower right ureter. The arrow points to the site of injury which is stenosed, angulated and displaced. The incompletely filled proximal ureter is widely dilated.

diversion was therefore urgently indicated to prevent further renal damage and to encourage continued resorption of the abdominal mass.

Accordingly, on April 1, 1957, a right nephrostomy was performed (JMS). The right kidney and upper ureter were found to be markedly dilated. The post-operative course was satisfactory and the patient was discharged nine days after surgery. The fistulous tract in the right lower quadrant closed soon after the nephrostomy was done, and the abdominal mass grew smaller in size.



During the next three months the patient improved considerably. He gained weight and strength. He experienced transient episodes of fever only when the nephrostomy tube was temporarily blocked.

When he was readmitted to the hospital on August 3, 1957, the right lower quadrant mass could no longer be palpated. An intravenous pyelogram continued to show dilatation of the right upper ureter and kidney. Urine cultured from the nephrostomy tube yielded *B proteus* and enterococcus. Hemoglobin determination was 11.2 Gm/100 cc. The white blood cell count was 16,800/mm<sup>3</sup> with 68 polys, 17 lymphs, 5 bands, 8 monos, and 2 eosinophils.

On August 8, 1957, a right ureteroplasty was performed (JMS). A right lower quadrant incision was made lateral to the old scar and the retroperitoneal space was entered. The lower third of the right ureter was of normal appearance. It was traced up to the level of the cecum where it was bound anteriorly by numerous adhesions to the peritoneum. Further upward dissection of the ureter brought into view a bulbous segment with markedly thickened walls. Proximally, the ureter was widely dilated. The bulbous enlargement was excised and an end-to-end anastomosis of the ureter was accomplished over a T-tube, suturing the dilated upper segment to the spatulated lower segment with interrupted 4-0 catgut sutures.

The postoperative course was uneventful. Some urinary leakage from the ureteroplasty site subsided in a few days. The pathology report of the excised segment was "active chronic ureteritis." The patient remained on nephrostomy and T-tube drainage. A gravity pyelogram performed August 28, 1957, demonstrated dilatation of the upper two-thirds of the ureter and a normal lower ureter. The transition region was not well delineated, but contrast medium readily passed downward to the bladder. The T-tube was removed on the 14th postoperative day. There was no urinary leak or other reaction. After progressive occlusion of the nephrostomy tube without incident, it was withdrawn on September 8, 1957. Several days later, an intravenous pyelogram still showed some dilatation of the right upper ureter and pelvis. However, in the course of the next six months there was progressive improvement in the function and appearance of the right kidney by urography. By March, 1958, intravenous pyelography delineated an essentially normal right kidney and upper ureter. The anastomotic site was displaced outward. The most recent intravenous pyelogram on September 12, 1960, three years after the ureteroplasty, demonstrated excellent function and a normal appearance of the right kidney and upper ureter (Fig. 4).

The patient has remained asymptomatic and in robust health. His blood pressure is within normal range. The urine is normal and the urine culture sterile.

#### DISCUSSION

The long course of the ureter, its frequent anomalous position, and ease of displacement exposes it to accidental injury in the course of intra-abdominal surgery (3, 4). The lower one-third of the ureter is the most common site of such

injury, particularly: 1. in the ovarian fossa, during adnexal surgery; 2. at the base of the broad ligament, when the uterine vessels are being ligated; and, 3. at the base of the bladder, during abdomino-perineal resection. The middle third of the ureter is rarely injured and then only when a retrocecal mass distorts the normal anatomy. Such a mass may be secondary to appendicular abscess, perfo-



FIG. 4. Intravenous urogram three years after right ureteroplasty demonstrates essentially normal renal structures on both sides.

rated carcinoma of the cecum, or may be the consequence of nonspecific inflammation or ileitis.

The incidence of operative ureteral injury at the above-mentioned sites can be materially reduced by careful dissection and meticulous hemostasis, preferably with a good segment of the ureter completely visualized. Whenever difficult gynecologic or abdomino-perineal surgery is anticipated, it is advantageous to obtain a preoperative intravenous urogram which will delineate the course of the ureter and establish its possible displacement and/or compression. An indwelling ureteral catheter of №5 or №6 calibre inserted prior to laparotomy aids

in the identification of the ureter during the surgical procedure, thereby considerably reducing the possibility of its injury. It may also serve as a splint for repair, should an accident occur.

The ideal time for recognition and correction of ureteral injury is before abdominal closure. Definitive repair is then usually easily and rapidly performed. Direct end-to-end anastomosis, either over an inlying catheter or a T-tube, is the preferred procedure. If the injury is close to the bladder and anastomosis of the severed ends of the ureter is not feasible, uretero-neocystostomy can be done, reimplanting the proximal ureter into the bladder. More elaborate and complicated methods such as the substitution of a section of ileum, are reserved for special situations (5, 6).

If the injury to the ureter is recognized only hours or days after operation, the type of management must be highly selective, taking into consideration the nature, site, and extent of injury and the status of kidney function. Diversion of the urine, preferably by nephrostomy, is often necessary, as was performed in our case. This prevents irreversible renal damage and allows sufficient time for subsidence of local reactions and inflammatory processes. When optimal response has occurred, the restoration of ureteral continuity can be attempted with greater expectation of a successful outcome (7, 8).

#### SUMMARY

A case of operative injury to the middle third of the right ureter resulting in stenosis and ureteral fistula is described. The considerable delay which intervened before the ureteral injury became evident and the presence of an inflammatory mass involving the local site, necessitated a preliminary diversion of the urine by nephrostomy drainage. After an interval of three months, during which time the mass subsided, excision of the involved segment of ureter and end-to-end ureteroplasty were performed.

Serial intravenous urograms over a three year period demonstrated that the kidney has been restored to an entirely normal status.

A brief discussion of the management of ureteral injury is presented.

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# FACTORS CONTRIBUTING TO CAUSES OF MENTAL ILLNESS AND HEALTH

## THE VIEWPOINT OF PSYCHIATRY AND PSYCHOANALYSIS

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"With regard to diseases, the circumstances from which we form a judgment of them are, — by attending to the general nature of all, and the peculiar nature of each individual, — to the disease, the patient, and the applications, — to the person who applies them, as that makes a difference for better or for worse, — to the whole constitution of the season, and particularly to the state of the heavens, and the nature of each country; — to the patient's habits, regimen, and pursuits; — to his conversation, manners, taciturnity, thoughts, sleep, or absence of sleep, and sometimes his dreams, what and when they occur; — to his picking and scratching; — to his tears; — to the alvine discharges, urine, sputa, and vomitings; and to the changes of diseases from the one to the other; — to the deposits, whether of a deadly or critical character; — to the sweat, coldness, rigor, cough, sneezing, hiccup, respiration, eructation, flatulence, whether passed silently or with a noise; — to hemorrhages and hemorrhoids; — from these, and their consequences, we must form our judgment."

Said some 2000 years ago by Hippocrates (1), the basic principles still hold today. A discussion of the etiology of illness, particularly in the area of psychiatry is an exceedingly complex matter. In order to understand current concepts of etiology it is essential to trace their historical evolution.

Basically all discussions of causes of mental illness from the earliest time to the present have implicated certain factors that might be generally categorized as heredity, constitution, life experience, and environment. From time to time a different weighting has been given to one or the other factors, but at all times all of the factors were considered as necessary components of a total situation which lead to a particular etiological theory. The cultural climate at any given time altered the content and perhaps the basic knowledge of any one of these factors, but the factors themselves have always been present.

Health and disease have always been of fundamental importance to mankind, and speculations, hypotheses, and theories relating to these matters have always been encumbered in direct proportion to our ignorance, with supernatural connotations. Health as a blessing, and illness as a punishment, are to this day beliefs that are present even in the most advanced of Western civilizations. The interpretation of the phenomena of mental disease have been particularly contaminated by such notions.

It has been stated that one of the great virtues of Hippocrates was that he attempted to place all illness, including mental illness, in a natural biological per-

From the Department of Psychiatry, The Mount Sinai Hospital, New York, N. Y. Presented at 1957 National Health Forum, Cincinnati, Ohio, March 20, 1957.



spective. Francis Adams (2), a translator of Hippocrates, in his discussion "On the Sacred Disease," in the section "The Argument" states that in spite of some contrary evidence he attributes this to be a genuine work of Hippocrates. This in itself is of no great significance since it is not really a question of credit. The work represents a point of view which is Hippocratic, and in this work particularly there is a de-emphasis of attribution of divine causality. There is an emphasis on the brain as the seat of the disease (in epilepsy) and "men ought to know that from nothing else but thence *from the brain* come joys, delights, laughter and sports, and sorrow, griefs, despondency, and lamentations. . . . " "And by the same organ we become mad and delirious, and fears and terrors assail us, some by night, and some by day, and dreams and untimely wanderings, and cares that are not suitable, and ignorance of present circumstances, desuetude, and unskilfulness. All these things we endure from the brain, when it is not healthy, but is more hot, more cold, more moist, or more dry than natural, or when it suffers any other preternatural and unusual affection. And we become mad from humidity (of the brain). For when it is more moist than natural, it is necessarily put into motion, and the affection being moved, neither the sight nor hearing can be at rest, and the tongue speaks in accordance with the sight and hearing. As long as the brain is at rest, the man enjoys his reason, but the depravement of the brain arises from phlegm and bile, either of which you may recognize in this manner: Those who are mad from phlegm are quiet, and do not cry out nor make a noise; but those from bile are vociferous, malignant, and will not be quiet, but are always doing something improper."

A classic compendium, unique in the history of psychiatry, is Burton's "Anatomy of Melancholy." This seventeenth century volume brings together both discriminately and indiscriminately practically everything that has been written on the topic of melancholia which includes the total spectrum of psychiatric illness. It can serve as a text of the then accepted ideas relating to the problem of etiology and nosology.

Under "Section 2, Member 1, Subsection 1—Causes of Melancholy. God a cause" he states, "It is in vain to speak of cures or think of remedies, until such time as we have considered of the causes; so Galen prescribes Glaucio: and the common experience of others confirms that those cures must be imperfect, lame, and to no purpose, wherein the causes have not first been searched as Prosper Calenus well observes in his tract about black bile to Cardinal Caesius; inso-much that Fernelius puts a kind of necessity in the knowledge of the causes, and without which it is impossible to cure or prevent any manner of disease" (4).

A mere listing of the various factors discussed as of possible etiological significance would perhaps be the best way to indicate the historical derivation of our twentieth century's ideas dealing with etiology. For instance, he states that general causes are either supernatural or natural. Supernatural are either from God and his angels or by God's permission from the Devil and his ministers. (Burton continues with a delightful digression on the nature of spirits, bad angels and devils and how they cause melancholy to which I can commend you.) To continue with the listing of causes—stars are a cause, old age a cause, parents a

cause by propagation, diet a cause, retention and evacuation a cause, air a cause, idleness, immoderate exercise, solitariness, sleeping and waking, passions and perturbations, force of imagination, sorrow, fear, shame and disgrace, envy, malice, hatred, emulation, desire of revenge, discontent, cares, miseries, ambition, concupiscible appetite, covetousness, love of gaming, self-love, pride, over-much joy, love of learning, study and outward causes "as first from the nurse. . . . . From a child's nativity, the first ill accident that can likely befall him in this kind is a bad nurse, by whose means alone he may be tainted with this malady from his cradle" (5). Education a cause, terrors and affrights, poverty and want, poverty and riches, loss of liberty, death of friends, worldly losses, curiosity and other accidents, and causes of melancholy from the whole body, inward or outward. It is quite evident from this list that with some slight changes in the actual wording that most of the items listed are considered to be of either primary or precipitating etiological significance today.

Benjamin Rush, who adorns the seal of the American Psychiatric Association, discusses the causes of madness under the headings of remote, exciting, and predisposing causes. It is of interest to note that Rush disposes of some previous etiological opinions and then proceeds to present his own. For instance, he calls the Hippocratic idea that "madness is due to a morbid state of the liver" an error (6). This also holds for diseases of the spleen. He draws attention to the idea that mental illness was thought to be due to a disease of the intestines. "The marks of inflammation which appear in the bowels in persons who have died of madness, have no doubt favored this opinion; but these morbid appearances, as well as all those which are often met with in the liver, spleen, and occasionally in the stomach, in persons who have died of madness, are the effects and not the causes of the disease" (7).

In this connection his explanation of the pathology found in these organs should be of interest in relation to present-day hypotheses of psychosomatic medicine. "Thus diseases in the stomach induce torpor and costiveness in the alimentary canal. Thus, too local inflammation often induces coldness and insensibility in contiguous parts of the body. Or, second, they are induced by the reaction of the mind from the impressions which produce madness, being of such a nature as to throw its morbid excitement upon those viscera with so much force as to produce inflammation and obstructions in them. That they are induced by one, or by both these causes, I infer from the increased secretion and even discharge of bile which succeed a paroxysm of anger; from the pain in the left side, or spleen, which succeeds a paroxysm of malice or revenge; and from the pain, and other signs of disease in the bowels and stomach which follow the chronic operations of fear and grief. That the disease and disorders of all the viscera that have been mentioned, are the effects, and not the causes of madness, I infer further from their existing for weeks, months and years in countries subject to intermitting fevers, without producing madness, or even the least alienation of the mind" (8).

Of particular interest is his objection to the idea that "madness has been placed exclusively in the mind. I object to this opinion, first, because the mind

is incapable of any operations independently of impressions communicated to it through the medium of the body. Second, because there are but two instances upon record of the brain being found free from morbid appearances in persons who have died of madness. . . . . Having rejected the abdominal viscera, the nerves, and the mind, as the primary seats of madness, I shall now deliver an opinion, which I have long believed and taught in my lectures, and that is, that the cause of madness is seated primarily in the blood-vessels of the brain" (9).

However, under the heading of remote and existing causes which he divided into two categories, those acting directly on the body and those acting indirectly on the body through the medium of the mind, he listed certain other factors such as malconformation and lesions of the brain, certain local disorders induced by enlargement of the bone, tumors, abscesses and diseases of the brain, particularly apoplexy, palsy, epilepsy, vertigo, and headache; insolation, certain odors, for instance the fumes of lead. Causes which act upon the brain in common with the whole body as gout, dropsy, consumption, pregnancy, and fevers of all kinds; the excessive use of ardent spirits, inordinate sexual desires and gratifications, onanism, great pain, extremely hot and cold weather; madness is induced by corporeal causes which act sympathetically on the brain such as certain narcotic substances, particularly opium, hemlock, night-shade, henbane, and aconitum; the suppression of any usual evacuation, such as the menses, lochia, milk, semen, or blood from the hemorrhoidal vessels; worms in the alimentary canal; "Madness is sometimes induced by what is called a metastasis of some other disease to the brain. These diseases are: 1) Dropsy. A case of madness from this cause is related by Dr. Mead, 2) Consumption. All the symptoms of this disease sometimes suddenly disappear, in consequence of the translation of morbid excitement to the brain" (10). St. Vitus' dance, the measles, hysteria, certain cutaneous eruptions; causes acting upon the body through the medium of the mind, such as intense study, frequent and rapid transition of the mind from one subject to another, imagination, extravagant joy, anger, terror, disappointed love, fear, grief. He places emphasis on heredity and predisposition, giving appropriate case illustrations.

The causes of mental disease as expressed by Rush fall essentially into the same categories as those implicated by earlier writers. The difference is only in the weight given to any specific category in terms of the state of medical knowledge of the day. Whereas Rush emphasizes diseases of the blood vessels of the brain, Battie in the middle of the eighteenth century emphasized the role of sensation, with the basic cause of insanity due to pressure on the nerves. It is of interest in this connection to quote Battie.

"Pressure of the medullary substance, the nearest in our apprehension to madness of all its known and remoter causes, most frequently and most effectually produces this its nervous effect, whilst it acts upon the contents of the cranium, as is evident from the cases above-mentioned. But, altho the brain is undoubtedly the principal seat of delusive sensation, nevertheless it is not the only one; forasmuch as the same sanguinary or serious obstructions are capable in any other nervous part of the body of exciting false ideas as well as in the brain, at

least to some degree and in proportion to the quantity of medullary matter there collected so as to be sufficiently compressed by such obstructions. Thus, the stomach, intestines, and uterus, are frequently the real seats of madness, occasioned by the contents of these viscera being stopt in such a manner as to compress the many nervous filaments, which here communicate with one another by the mesenteric ganglia, and which enrich the contents of the abdomen with a more exquisite sensation. Thus the glutton who goes to-bed upon a full stomach is hagridden in his sleep. Thus *Men prove with child as powerful fancy works*: And patients truly hypochondriacal or hysterical refer that load of uneasiness they feel in their bellies to some imaginary object, which if it really existed and acted upon their senses would excite the very same idea" (11).

Another writer in the early nineteenth century concerned himself with the problem of "Neurotica or Diseases of the Nervous System." John Mason Goode in his 5 volume work on "The Study of Medicine with a Physiological System of Nosology" in the 2nd American edition, 1824, stated, "But the nervous organ in its most elaborate and perfect state, as in man, is not only the seat of sensation and motion, but of intelligence; it is the instrument of communication between the mind and the body, as well as between the body and the objects by which the body is surrounded. And as a failure or irregular performance of its function in various ways, lays a foundation for an extensive division of corporeal diseases, so a like failure or irregularity of performance in other ways lays a foundation for as numerous a train of mental maladies.

"Of the nature of the mind or soul itself, we know little beyond what *Revelation* has informed us; we have no chemical test that can reach its essence; no glasses that can trace its mode of union with the brain; no analogies that can illustrate the rapidity of its movements" (12).

In addition to disease of the brain as a primary cause, he held that many other factors were either accidental or accessories, particularly in melancholia. "Grief, and particularly for the loss of friends, discontent, severe disappointment, the dread of some real or imaginary evil, a violent and long continued exertion of any of the passions, and deep uninterrupted study, have frequently proved accidental causes or accessories of this variety of melancholy, where the peculiarity of the constitution has formed a predisposition, and have sometimes produced it even where no such predisposition can be traced. In like manner it has proceeded from immoderate exercise; insolation, or long exposure to the direct rays of the sun; sudden transitions from heat to cold; powerful stimuli applied to the stomach."

It seems quite clear from all that has been cited above that the areas within which the etiology of mental disease were thus found were considered from the earliest times to be as stated; heredity, constitution, life experience which included relationship of man to his environment, and incidental factors like trauma, somatic illness and infection, constitution and temperament, each author giving due weight to one or the other particular aspect of these factors in terms of the scientific climate of his time.

It is of interest in this connection that the current state of a particular culture



or civilization has more or less always been implicated as a causative factor. I hope at some future date to discuss this at some length since I believe that culture channels instinct. Perhaps Bucknill and Tuke's statement in 1858 may serve as a paradigm. "And regarding the question in an abstract and theoretical point of view, we should certainly be disposed to expect that the development of civilization, in its highest and widest sense, would conduce to the mental health of any people subjected to its influence. But practically, we submit, that, in consequence of the abuse of the very blessings attendant upon the progress of civilization, and of the temptation which civilization offers to overtask the mental faculties; and, lastly, in consequence of the greatly increased degree in which the emotions are developed, the result is, that an advanced civilization tends to increase the number of the insane. 'I am not one of those modern philosophers,' says Dr. Rush, 'who derive the vices of mankind from the influence of civilization; but I am safe in asserting that their number and malignity increase with the refinements of polished life. To prove this, we need only survey a scene too familiar to affect us; it is a bedlam, which injustice, avarice, pride, vanity, and ambition, have filled with inhabitants'" (14).

Perhaps one of the psychiatrists who is most misconstrued at the present time in terms of his historical importance is Kraepelin (15). He is generally cited as the individual who made a major contribution to psychiatry primarily in terms of classification and whose concept of etiology remained primarily in the area of brain disease. Whether this is a result of his lack of availability in English or not is a question. It seems to me to be of great importance to undo this error. In Volume I of his 8th edition, he deals with the problems of etiology at great length, and again a mere statement of the factors which he takes into account is of extreme interest.

He divides causative factors into two main categories: outer causes and inner causes or "predisposition." Amongst the outer causes he discusses brain disease, nerve disease, operative trauma, exhaustion, infectious illnesses, metabolic illnesses, poisonings, organic disease, difficulties in the sexual life and psychic causes which include mood changes, overwork, captivity, worry and catastrophes, psychic contagion; and under inner causes and predisposition there is age, sex, racial factors, climate, general circumstances of life, calling, and then heredity, developmental difficulties, degeneration, upbringing, and personal uniqueness.

An historical note of some significance is worthy of restatement. In the section devoted to mood changes he makes the statement that forgotten experiences may result in "mood disturbance" and notes that Breuer and Freud occupied themselves with this aspect of the problem, and particularly that they emphasized early sexual experiences as general causes of hysteria. In another statement he agrees that Freud's theory in relation to repression and the importance of early life experiences are significant, adding only that there was perhaps an overemphasis on the role of infantile sexuality. In a discussion of the psychiatric conditions precipitated by captivity in relation to the Ganser syndrome, he feels that some of the symptoms manifested in that illness make it necessary to think of repression phenomena in Freud's sense.

Kraepelin, Bleuler, and Freud were contemporaries not only in a chronological sense but in a psychiatric one. Whereas Bleuler, especially in reference to schizophrenia, considered that illness to be primarily on an organic basis, he nevertheless in dividing symptomatology into primary and secondary ones took cognizance to a much greater extent of Freud's contribution. A fundamental difference between Kraepelin and Bleuler lies in Bleuler's acceptance of Freud's concept of the Unconscious in terms of its fundamental laws of the primary process which would lead to an understanding of the meaning of the content of delusions and other symptoms. He did, however, note that at that time (1911) there was a preference for toxic theories with the statement that "the only support for the first group (*i.e.*, autotoxic group) is provided by Berger's experiments. He discovered that the blood of catatonics contained a specific substance which had a stimulating effect on the cortical motor centers of dogs and which was not present in other diseases including the hallucinatory confusional states. Since, at present, catatonia cannot be differentiated from these confusional states and since the number of experiments made was far too small, these investigations are as yet entirely inconclusive. It is also questionable, whether the toxin was not of an accidental or secondary nature" (16).

This is interesting in view of the recent work by Heath. It should be remembered that Jung in his monograph on "The Psychology of Dementia Praecox," first published in 1906, in which he adopted Freud's psychoanalytic psychology as his basic frame of reference nevertheless stated that perhaps the only difference between hysteria and schizophrenia was that schizophrenia was due to a toxin. He recently, according to the newspapers, returned to the toxic theory of schizophrenia.

In Bleuler's chapter on the causes of disease, he discusses heredity, the question of anlage, the age period, infectious diseases, gravidity in the puerperium, organic cerebral disturbances "have to receive special attention;" an individual's dissatisfaction with life. Of importance is the statement that "as yet we cannot answer the question whether there are psychic causes for schizophrenia. However, it is probably to be answered in the negative." His conclusion was that psychic experiences undoubtedly affect the schizophrenic symptoms but cannot really produce the illness.

If one utilizes schizophrenia as a paradigm for the psychoses, it becomes clear that to Bleuler the disease is primarily due to some process on a somatic basis, the nature of which is as yet unknown. Nevertheless, all the other factors implicated may have some significance in relation to the course of the illness.

The contribution of Freud\* to the problem of etiology is unique in several senses. Psychoanalysis is biologically based and takes into account heredity, and, particularly, constitutional factors. The weighting of these factors has varied from time to time, but they have always been basic to Freud. Several contributions of psychoanalytic theory are particularly significant. Whereas the concept of an unconscious in the sense of psychic experiences of which an indi-

\*The contributions of Freud in this area are fundamental. They appear in almost every one of his papers and it would be difficult to single out one or more of his papers to point up the contributions. The reader is referred to his *Collected Works*.

vidual was no longer aware had long been part of psychiatry and philosophical thought; nevertheless the system Unconscious of Freud was unique in the sense that it took on an added dynamic force that the Unconscious functioned in terms of a primary process which involved timelessness, the pleasure principle; no negation, exemption from mutual contradiction; is not related to reality; there can be a substitution of psychic for external reality, there is mobility and displacement which permits of an adaptation which leads to symptom formation in the total functioning of the organism. In other words, this is not a filing cabinet area for forgotten experiences.

Another contribution of great importance is the genetic point of view in a very specific sense. The importance of life experiences from the earliest time is emphasized in relation to an instinct theory. Conflict and the techniques for the resolution of conflicts become of paramount importance. The zonal hypothesis makes for a specificity of character formation and psychiatric symptomatology so that there is a relationship between the phenomenology of the manifestations and the developmental level at which conflict and fixation take place.

Concepts of etiology in psychoanalysis are related to all these factors in a very specific sense. The complexity of basic psychoanalytic theory makes it impossible to even summarize all the factors that are considered to be of etiological importance, except in the most general terms. In a certain sense Freud's theories served to integrate all previous knowledge in the field of human behavior.

It is of interest to note that in this country Adolf Meyer emphasized the multiple factors involved in the development of the human organism particularly in relation to personality structure. He gave them different weightings and never recognized a system Unconscious in Freud's sense. He was, however, in great sympathy with some of the basic concepts of Freud. One of Meyer's great contributions was his emphasis on the uniqueness of each individual and "the experiment in nature" which each psychiatric reaction represented.

Growing out of the above background there has been a trend in recent psychiatric thinking which has led to two related trends, each of which can be epitomized briefly as follows.

Romano (17) in his introduction to the volume on "Adaptation" which contains the dedicatory papers presented at the opening of the psychiatric unit of the Strong Memorial Hospital states as follows: "However, a concept central to biology, psychology, and sociology, is that of adaptation. This was chosen as the theme of today's exercises as it will enable each of the scientists to present his specific body of knowledge—from cellular organization to social structure—in terms of the genesis, nature and development of adaptive devices and of their success or failure in maintaining balance and in mastering stresses, whether these stresses arise from within the cell, organ, organism, or group of organisms or from without."

The other trend is typified by the statement appearing in Grinker and Robbins' (18) book "Psychosomatic Case Book," at the end of the chapter on "Modern Theoretical Concepts." Although this is stated in relation to the psychoso-

matic field it is also true in regard to the area of psychiatry. "The time is ripe, it seems to us, to consider the psychosomatic field not as a fractured, disjointed, and isolated series of observational sectors but as a *total integrated field* which can be studied from many points of view by many disciplines. We feel that all types of observation and all techniques of measurement are essential but are adequate only if they can be integrated in terms of the total field concept."

When one looks back with an historical perspective, it becomes clear that each of the factors considered to be of importance have in principle been so considered since the earliest times. Advances have been made in each one of the areas by specialists in that particular field. The psychiatrist as a physician now has the role of interrelating, integrating, and synthesizing the knowledge that comes from many disciplines, each important in its own right, but each when standing alone presenting a highly sectarian point of view. Looked at from this position it becomes clear that it can only be the psychiatrist in his role as a physician who is able to understand the "person as a whole."

The disciplines represented in this symposium, each standing by itself, can only enrich our knowledge in certain aspects of the problems involved. It is only when one combines all of these contributions that one approaches in a very tentative way the beginning of an understanding of the many variable factors involved in the etiology of mental disease.

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# AUTOIMMUNITY IN THE PATHOGENESIS OF HUMAN DISEASE

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The term immunity usually implies defence against repeated infections, but it covers many activities in addition to this. Thus the self-recognizing function of the body is an essential part of immunity, since every vertebrate organism must be capable of differentiating vast numbers of antigenic configurations as belonging either to the body's own material, "self," or to foreign material, "non-self."

The tissues and cells concerned in the various immune reactions properly constitute an organ or system, characteristically dispersed in many sites of the body, but with particular concentrations in the spleen, lymph nodes, thymus and alimentary tract. This system is of mesenchymal origin and includes lymphocytes, plasma cells, reticulum cells and intermediate forms; it may be referred to morphologically as the lymphoreticular system and functionally as the antibody producing system, provided the range of immunological functions is implicitly covered by the latter term.

The pathological changes and the functional disorders of this system may be listed as follows:

1. Developmental failure or atrophy, resulting in agammaglobulinemia;
2. Neoplasia, occasionally with synthesis of aberrant antibody-type globulins, as in multiple myeloma, lymphosarcoma and macroglobulinemia;
3. Abnormal reactivity to antigens introduced from the exterior, as in allergy, anaphylaxis and hypersensitivity;
4. Autoimmune disease, the essence of which is a breakdown of the process of self-recognition, so that immune responses are directed not only to foreign material but also to "self" components.

Diseases resulting from abnormal functioning of the antibody producing system are often referred to as "immunopathies."

Immune reactions operate at different functional levels, including classical antibody, non-precipitating antibody or reagin which is characteristic of hay fever, and cell-based delayed hypersensitivity reactions. It is usual to describe specific immunity in terms of antibodies which may be defined as soluble proteins capable of uniting with antigen and producing an aggregation reaction in the form of a visible precipitate or some formal equivalent, subject to the qualification that "incomplete" non-precipitating antibodies may exist. However, it is important to recognise that immune phenomena include all three types of

Presented December 5, 1960 before the Gastroenterology Division of the Department of Medicine, The Mount Sinai Hospital, New York, N.Y. Aided by a grant from the National Institute of Arthritis and Metabolic Diseases.

\* From the Clinical Research Unit of the Walter and Eliza Hall Institute and the Royal Melbourne Hospital, Victoria, Australia, working with the aid of a grant from the National Health and Medical Research Council of Australia.

response and probably others not yet clearly characterized. Delayed hypersensitivity is a function of lymphoid cells, and a feature of modern immunology is its deep interest in the cells—immunologically competent cells—which are concerned with various immunological functions, of which antibody production is only one.

Self-recognition and antibody production to “non-self” material are now thought of in terms of two main groups of theories known as the “instructive” and “selective” theories (Fig. 1). The more conventional instructive theories, Lamarckian in their implications, stipulate that an antigen induces a change in the pattern of protein synthesis of a cell; according to some of these theories, this acquired change is transmitted to the cell progeny. Selective theories, which take an essentially Darwinian approach, may be exemplified by Burnet’s clonal selection theory as follows (1, 2).

1. During differentiation in embryonic life, a sufficiently large number of clones of potential antibody forming cells develops to provide all of the immunological patterns needed during postnatal life.
2. Clones carrying patterns corresponding to accessible antigenic determinants in the body are eliminated during embryonic life, presumably by destructive contact with antigen at a hypersensitive phase of their development.
3. Thus the remaining population of antibody producing cells, or better, immunologically competent cells, will correspond to (a) antigenic determinants *not* present in the body, and (b) determinants limited to inaccessible regions of the body.
4. Cells of each clone carry one or two antibody patterns—however, there exists the possibility of some form of transfer of information between clones.
5. The function of an antigenic determinant in mature animals is to stimulate into activity those cells already preadapted to react with that determinant.
6. Antigenic contact may cause (a) inhibition or destruction, (b) proliferation, and (c) the plasma cell phase with synthesis and liberation of antibody.
7. Clones carrying new immunological patterns arise in postnatal life, probably by somatic mutation.
8. Newly developed clones corresponding to self antigens are termed forbidden because of their self-reactive character.
9. Normal health demands the elimination of forbidden clones by processes akin to homeostasis—these may include destructive contact with antigen in excess.
10. Failure of suppression of forbidden clones produces autoimmune disease (Fig. 2).

Although our incomplete knowledge precludes a concise definition of autoimmune disease, five “markers” of autoimmunity can be defined—(a) hypergammaglobulinemia, (b) circulating autoantibodies, (c) lymphoid hyperplasia,

(d) responsiveness to cortisone and (e) association of the lesion under consideration with other lesions attributable to autoimmunity.

Diseases fulfilling some or all of these markers form two well defined groups. The first group is associated with organ-specific inaccessible autoantigens—the “inaccessible autoantigen” group. It is exemplified by Hashimoto’s thyroiditis, and probably includes “allergic” encephalomyelitis, sympathetic ophthalmia, orchitis, and other conditions wherein the specific autoantigen has not yet been identified. In the second group, circulating autoantibodies are demonstrable to

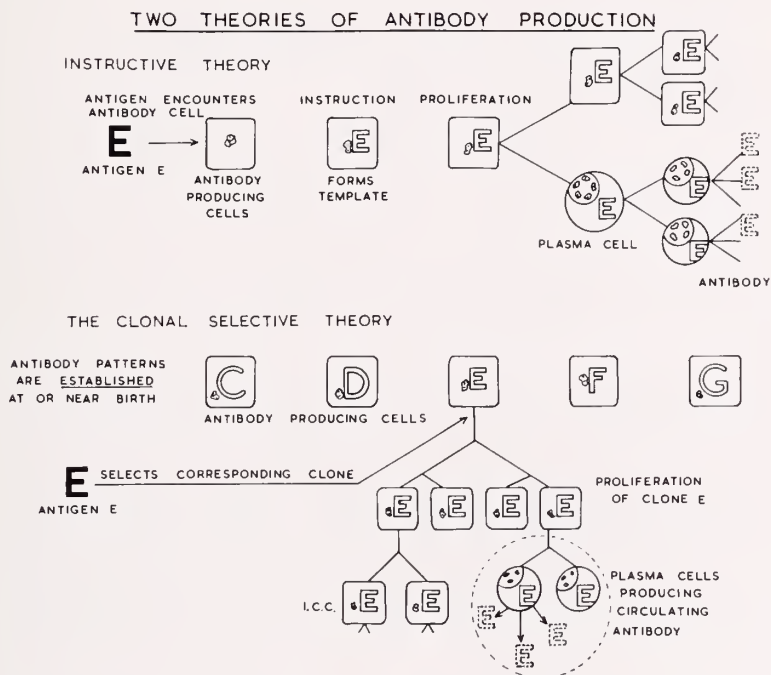


Fig. 1. Diagrammatic representation of instructive and selective theories of antibody production.

I.C.C.—immunologically competent cell.

nonorgan-specific accessible autoantigens. This “accessible autoantigen” group includes systemic lupus erythematosus (SLE), rheumatoid arthritis, hemolytic disease, and possibly polyarteritis nodosa, dermatomyositis, salivary and lacrimal disease of the Sjögren-Miculicz type and lupoid hepatitis.

“Inaccessible autoantigen” group: Here we are concerned with true autoantigens which are derived from body constituents normally well shielded from the ordinary wear and tear of the body. Examples include thyroid, neural, uveal and testicular antigens, and it is the failure of these antigens to initiate tolerance in embryonic life that accounts for their latent pathogenicity. This type of autoimmunity is reproducible experimentally with specific homologous and even autologous organ extracts injected with appropriate adjuvants.

In Hashimoto’s thyroiditis, which best exemplifies diseases due to inaccessible



autoantigens, there is goiter and thyroid insufficiency, characteristically in middle-aged to elderly women. The markers of autoimmunity pertain, including organ-specific autoantibodies in the serum; in particular there may be coexisting disease of autoimmune character, including hemolytic anemia, rheumatoid arthritis or chronic hepatitis (3).

According to earlier concepts, infection or other trauma initiated autoimmune thyroiditis by causing a leak of thyroglobulin which stimulated the production of circulating antibodies capable of reacting damagingly with thyroid com-

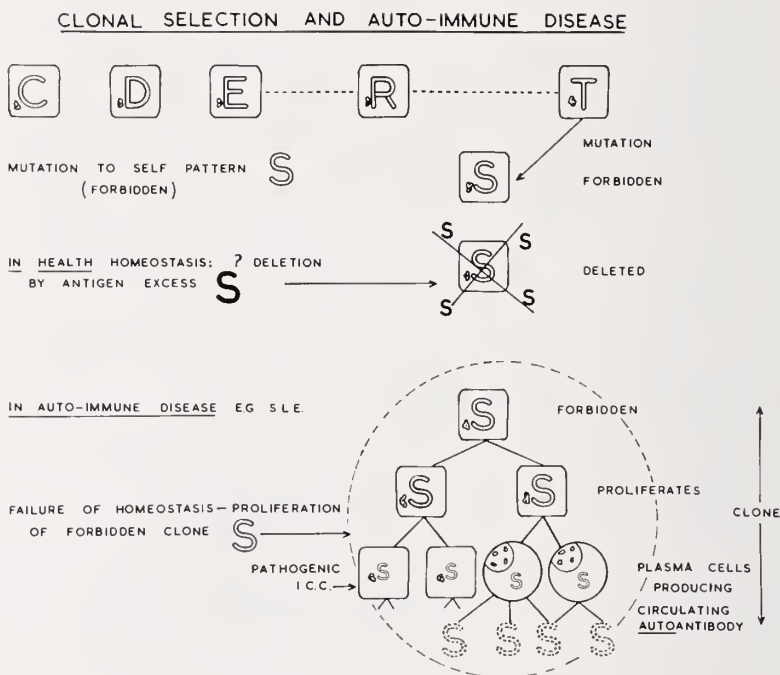


Fig. 2. Clonal selection theory: autoimmune disease results from proliferation of a "forbidden" clone.

I.C.C.—immunologically competent cell.

ponents, so releasing fresh antigen and thus creating a self-perpetuating "vicious circle" disease. We have termed this process "autoclasia" or self-breaking down. However, belief in the rôle of circulating autoantibodies has been disturbed by the finding of high titers in the absence of histologically demonstrable thyroid disease and a poor correlation between antibody titers and the intensity of the disease. It is now thought that immunologically competent cells cause tissue damage in thyroiditis and in other members of this group. The transfer of "allergic" encephalomyelitis to rats by injecting immunologically competent cells is therefore of considerable interest (4).

Since "inaccessible" antigens behave virtually as foreign antigens, autoimmune diseases attributable to such antigens offer no evidence favouring or dis-

crediting instructive or selective theories of antibody production. Thus, on instructive theories, an inaccessible antigen such as thyroglobulin could act as a template for autoantibody synthesis by virtue of being extrinsic or "foreign." On the clonal selection theory, liberated thyroglobulin or microsomal antigen would activate the corresponding clones of cells which have either persisted from embryonic life or arisen as a result of subsequent mutation (Fig. 3).

Clones reactive with thyroid constituents must become established with some frequency, as judged by the appearance of lymphoid collections in the thyroid

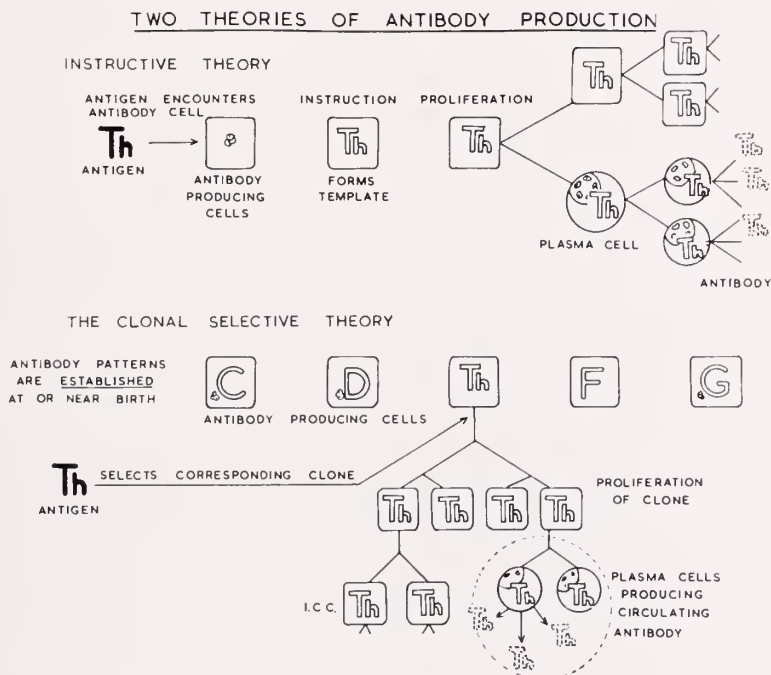


FIG. 3. Autoimmunity in thyroid disease: antibodies to inaccessible thyroid antigens (Th) can be accounted for by either instructive or selective theories of antibody production.  
I.C.C.—immunologically competent cell.

gland and antibody in the serum in various thyroid and nonthyroid diseases, yet destructive thyroiditis is an uncommon event. When antibody production is the only response and there is no disease, the term autoimmune reactivity is applicable. However, in certain individuals predisposed to immunopathy, there will be colonization of the gland by immunologically competent cells and a persistently destructive or autoelastic thyroiditis supervenes. To account for the progressive quality of the disease, its rarity and its great predominance in elderly women, additional changes must be postulated, enabling the clone to escape from some type of control and assume heightened aggressiveness and colonizing ability. It is therefore of some interest that Hashimoto's disease occasionally terminates in lymphosarcoma (5). Perhaps the special virtue of an adjuvant, as used in the experimental production of autoimmune disease, is its ability to

confer this heightened aggressiveness and colonizing ability on the appropriate immunologically competent cells.

"Accessible autoantigen" group: With the second group of autoimmune diseases, which includes lupus erythematosus, rheumatoid arthritis and hemolytic anemia, an entirely different situation occurs in that antibody is developed to highly accessible nonspecific antigens. These antigens include desoxyribonucleic acid (DNA) and other constituents of nucleoprotein, denatured gamma globulin, and a superficial erythrocyte antigen. It is noteworthy that experimental counterparts of diseases in this group cannot be readily induced in animals.

It seems most unlikely that these accessible and widely distributed antigenic determinants could become effective antigenic stimulants to normal antibody producing tissues, as would be demanded by instructive theories of antibody production. Admittedly, there have been suggestions that, in "hypersensitive" subjects, heterologous antigenic stimulation could elicit autoantibodies reactive with autologous compounds. Thus, bacterial DNA might elicit an antibody which would react damagingly with the individual's own DNA. Another suggestion is that body components become altered by disease and therefore rendered auto-antigenic, with the postulated altered antigen then provoking autoantibodies reactive with normal body components. There is no real experimental support for these suppositions and the concept of heterologous stimulation of an autologously reactive antibody is difficult to accept.

In terms of the clonal selection theory, antibody formation to accessible antigens of the body is determined by some abnormality in the antibody producing lymphoid tissues permitting clones carrying self-reactive patterns—forbidden clones—to emerge and escape from the normal homeostatic control. Thus there might be hypermutability with the emergence of clones abnormally resistant to homeostatic control or, alternatively, weakness of homeostasis. Both could allow establishment of forbidden clones. Forbidden clones with the greatest opportunity to survive and flourish would be those directed against the commoner antigenic determinants of the body, such as nucleoprotein and the red cell surface.

Of all the autoimmune diseases, lupus erythematosus shows the widest distribution of lesions and range of circulating autoantibodies (6-11), this being indicative of a generalized failure of immunological homeostasis. Thus, there are autoantibodies reactive with whole nuclei, DNA, nucleoprotein, histone, a phosphate buffer extract of nuclei, mitochondria and soluble cellular proteins. This immune reactivity is demonstrable by all the conventional methods, including precipitation, complement fixation, tanned cell hemagglutination, immunofluorescence and passive cutaneous anaphylaxis. Antinuclear and anticytoplasmic titers are highest in the active phase of the disease and diminish during remissions, but titers do not closely follow phases of the disease. The antibodies are widely heterospecific in that the anti DNA antibody reacts equally well with DNA from human, animal and bacterial sources; the anticytoplasmic antibodies are similarly reactive with human and other mammalian tissues. Cutaneous sensitivity to leucocytes is also demonstrable. There is no evidence that the circulating autoantibodies have cytopathogenic effects.

The lesions of SLE may be randomly distributed in any tissue of the body. The lesions comprise fibrinoid degeneration of collagen and intercellular connective tissues, diffuse vasculitis, hematoxylin body formation, lymphoid hyperplasia and infiltration of affected tissues with lymphocytes and plasma cells. Which, if any, of these represents the fundamental lesion of SLE is controversial. According to our present concepts, lymphoid collections in target tissues would be regarded as representatives of pathogenic forbidden clones.

The development of lupus erythematosus may be determined firstly by genetic predisposition, secondly by constitutional factors, and thirdly by accidental initiating factors such as tissue trauma. In genetically predisposed individuals, immunologically competent cells can pass readily into an aggressive proliferative phase, so permitting the further emergence of forbidden clones, limited in number only by the availability of potential antigenic determinants in the body. Constitutional factors affecting immunological homeostasis may include endocrine balance, neurogenic influences, and the ageing process: these await further evaluation.

Lymphoid tissue, which is the main site of immunologically competent cells in the adult, contains the most freely available of all the potential antigens of the body—nuclear fragments of lymphocytes. Hence antinuclear clones are particularly likely to develop in lymphoid tissues. However, antecedent damage may allow forbidden clones to undergo maximal development in other sites. In lupoid hepatitis, for example, forbidden clones are enabled to colonize the liver after it has been damaged, particularly by viral infection. Once initiated, SLE and related conditions are essentially self-perpetuating, since immunologically provoked tissue damage liberates a further supply of antigenic determinants, giving continuing stimulation to the appropriate forbidden clone.

A high proportion of patients with rheumatoid arthritis have the "rheumatoid factor" in the serum. This is an autoantibody which agglutinates red cells or inert particles when these are coated with mildly denatured gamma globulin (pGG). The factor may exist in the serum combined in part with antigen as a complex which sediments as a 22S component in the ultracentrifuge; this complex can be dissociated into the antibody, a 19S macroglobulin, and a 7S gamma globulin which is the antigen (12). This reaction has given rise to a variety of diagnostic laboratory procedures for rheumatoid arthritis. However, we have found that some apparently "normal" individuals and patients with diseases other than rheumatoid arthritis may have antibody to pGG, often in very high titer.

The significance of denatured gamma globulin as an antigenic determinant is uncertain. Experimentally, an anti-gamma globulin antibody develops (a) in rabbits immunized with homologous gamma globulin of different allotype injected with Freund's adjuvant (13); (b) to weak titer in rabbits immunized with autologous gamma globulin (14); and (c) in rabbits immunized with bacterial antigens (15). It is of interest that the antibody titer of serum to heterologous antigen may be greater than to homologous antigen (14).

Presumably any deposition of antibody gamma globulin on bacterial antigens could result in extensive formation of the pGG antigen. Moreover, since the pGG antigen is produced only after immunological maturity, it could be treated by



the body essentially as a foreign or extrinsic antigenic pattern, although this does not account for its particular incidence in rheumatoid arthritis. It seems more reasonable to assume that the antigenic determinant of DGG is potentially so common that immunological activity against it should be suppressed under conditions of health.

Local cellular accumulations may be significant in the pathogenesis of rheumatoid arthritis. Thus, fluorescein-labeled antibody studies have shown the synovial villi of affected joints to be densely infiltrated with plasma cells which are producing an antibody with the same specificity for DGG as the circulating rheumatoid factor, and the related lymph nodes also contain such cells (16). Although the occurrence of rheumatoid arthritis in patients with agammaglobulinemia (17) suggests that DGG could be a secondary rather than a primary autoantigen, the established disease probably depends in part upon the reactivity of forbidden immunologically competent cells with denatured gamma globulin.\* Thus the deposition of DGG becomes the focal point of the disease, since to it are attracted pathogenic forbidden clones which react with DGG deposited in joint structures, causing further damage and a self-perpetuating disease.

Autoimmune hemolytic disease can be separated from the group of acquired hemolytic anemias on the basis of serologic evidence of antibody globulins being attached to the patient's red cells. The commoner "warm" antibodies are active at 37°C and are well absorbed onto the patient's red cells *in vivo*; cold antibodies, which were present in nearly thirty per cent of Dacie's cases of autoimmune hemolytic anemia (18), are active at temperatures from 5° to 30°C, and are poorly absorbed onto red cells *in vivo*.

Warm antibodies are present in low concentration in the serum but may be eluted from the patient's red cells and behave in the laboratory as incomplete antibodies. They are usually nonspecific and agglutinate all human red cells independently of the known blood group antigens. Occasionally the antibody is specific in that it reacts with a particular antigen, usually *e*. Cold antibodies are also nonspecific and even react with the red cells of certain animals. They are poorly absorbed, and hence are present in large quantities in the serum, producing peaks in the electrophoresis pattern; at low temperatures, agglutinin titers may exceed 64,000 (18). Cold antibodies are of high molecular weight and are thus macroglobulins, so that cold antibody hemolytic anemia may be identifiable with the syndrome of macroglobulinemia (19), wherein bizarre patterns of autoantibody behaviour† may be exhibited.

Cold antibody hemolytic anemia is more clearly related to mutational changes in lymphoid tissues than is the warm antibody type, since cold agglutinins may resemble pathological paraproteins in each being antigenically distinguishable (20). This is an exceptional finding in that antibody globulins are not regarded as having individually specific characteristics. Thus Mehrotra considered that

\* Some cases of acquired agammaglobulinemia could even be the result of immunologic destruction of plasma cells by forbidden clones of lymphoid cells with a specificity for 7S gamma globulin.

† Sera from four of our twelve cases of macroglobulinemia reacted to high titer either with cytoplasmic antigens in the autoimmune complement fixation test, or to thyroglobulin.

cold antibodies represent "synthesis of abnormal proteins rather than an immune response on the part of normal antibody forming tissues" (20).

Idiopathic autoimmune hemolytic anemia may be determined by genetic factors, or may be related to the development of SLE or neoplastic change in lymphoid tissues. When acute hemolytic anemia complicates primary atypical pneumonia and infectious mononucleosis, we must assume that viral infection produces a local abnormal environment in lymph nodes favouring the development of clones which would be "forbidden" elsewhere.

In idiopathic hemolytic anemia, the spleen is the main site of red cell destruction and red cell antigens will therefore be most freely available there; hence the great majority of cells making up the forbidden clone should be concentrated in the spleen. Again a vicious circle can be visualized if hemolysis becomes particularly active, since disintegrating red cells will provide fresh antigenic determinants and further stimulate the forbidden clone. The beneficial effect of splenectomy may be due to breaking this vicious circle.

Immune processes may determine "idiopathic" thrombocytopenia, since the thrombocytopenic factor in the blood can be frequently related to platelet agglutinins which are apparently autoantibody in type (21). It is also significant that idiopathic thrombocytopenic purpura often accompanies acquired hemolytic anemia and, for a time at least, it may be the lone manifestation of SLE.

The status of rheumatic fever and glomerulonephritis is uncertain. Current opinion is that a streptococcal toxin is produced in the throat and passes to, and is fixed in, certain tissues including the renal glomerulus, synovia and endocardium; the immune response develops to the point where antibody circulating in the blood stream encounters streptococcal antigen still present in the tissues and damage occurs as a result of this encounter.

With regard to rheumatic fever, Burnet (22) has suggested that stimulation associated with streptococcal infection of the pharyngeal lymphoid tissue allows the development there of a forbidden clone specifically reactive with a determinant present in synovial and endocardial tissues. However, since continued presence of streptococcal infection in the pharynx appears to be necessary, this does not exemplify the persisting autoaggressive behaviour of forbidden clones in general.

Acute glomerulonephritis is related to pharyngeal infection with specific nephritogenic streptococci: whether glomerular damage be of toxic or immunologic origin, the condition is usually self-limited and autoimmunity need not be invoked. On the other hand, any explanation of the pathogenesis of subacute membranous glomerulonephritis must account for the persistence and progression of the disease in the apparent absence of any continuing provocative agent. A forbidden clone possibly develops capable of forming autoantibody to a determinant in the glomerular basement membrane, since the general character of the glomerular lesions points to damage by circulating antibody or antigen-antibody complexes; one clue is the build-up of gamma globulin in the glomerulus as shown by fluorescein-labeled antibody studies.

The pathogenicity of immunologically competent cells is now being investigated on the basis of experimental models utilizing the "graft versus host" reac-

tion. These include the "runt" syndrome produced by inoculation of adult cells into neonatal animals of a different strain, the Simonsen phenomenon in embryo chicks and the analogous reaction of donor fowl leucocytes with the chorio-allantoic membrane of the chick embryo (23), F 1 hybrid disease, and secondary or homologous disease in x-irradiated animals. These experimental situations, wherein the recipient or host subject eventually succumbs to an onslaught of immunologically competent donor cells, may be likened to the effects produced by forbidden clones in human autoimmune disease.

Although the picture of autoimmune disease is still constructed with a liberal amount of speculation, facts are fast emerging from the laboratories and from the clinical field which confirm our belief in the great importance of this disease process to man. With increasing knowledge we may reasonably expect some improvement in treatment of these conditions, but the more interesting prospect is that ways may be found whereby individuals with a genetic predisposition to autoimmune disease can be protected against its clinical emergence.

#### SUMMARY

1. The reality of autoimmunity and autoimmune disease must be accepted on the basis of serological and histological findings in human subjects and laboratory models in animals. Since the facts and theories relating to autoimmunity must fit our interpretations of antibody synthesis under naturally occurring conditions, autoimmune disease must be examined from the viewpoint of the current instructive and selective theories of antibody production. Whereas instructive theories do not adequately explain autoimmunity, particularly where accessible antigens are concerned, autoimmune disease fits well into the framework of Burnet's clonal selection theory.
2. Autoimmune diseases may be (a) of the "inaccessible" antigen type, such as Hashimoto's thyroiditis and encephalomyelitis, and (b) of the "accessible" antigen type, wherein antibodies are demonstrable to nucleoprotein, the erythrocyte surface and denatured gamma globulin, as in lupus erythematosus, hemolytic anemia and rheumatoid arthritis.
3. In autoimmune disease, the behaviour of immunologically competent cells is more important than the behaviour of autoantibodies which, except for hemocytolytic antibodies, may be pathogenetically irrelevant. However, the damaging effects of circulating antigen-antibody complexes on the kidney and elsewhere are still to be evaluated. Possibly the most important implication of an autoantibody is its indication that pathogenic immunologically competent cells of the same specificity are also present in the body.
4. The important genetic factor in autoimmune disease may be expressed via an increased responsiveness of antibody forming tissues to various types of antigenic stimulation and by an increased tendency to mutations to self-reactive or "forbidden" clones of immunologically competent cells. In addition, forbidden clones must escape from some homeostatic control, and hence fail to be eliminated as occurs in health.

5. Trauma may initiate autoimmune disease by exposing intracellular antigenic determinants to forbidden clones, so providing a proliferative stimulus. However, pathogenicity of forbidden clones also implies a transition to an aggressive nonresponsive phase, somewhat suggestive of a conditioned neoplastic disease of the lymphoid tissues.
6. Contact between forbidden immunologically competent cells and host cells carrying the corresponding determinant will result in damage to both, with liberation of the pharmacologically active substances associated with inflammatory reactions. Hence, more antigenic determinants will be brought into contact with immunologically competent cells, and there will be more extensive access of cells into the target tissue. Secondary effects will be heightened aggressiveness and further mutations to additional forbidden patterns: the potentialities for a vicious circle or chain reaction type of self-perpetuating disease are readily apparent.
7. Laboratory models are providing new insight into the behaviour of pathogenic immunologically competent cells. Such insight may enable us to devise better methods for suppressing the forbidden clones of cells responsible for human autoimmune disease.

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## HERPES ZOSTER AND VARICELLA OCCURRING IN SIBLINGS FOLLOWING CONTACT WITH CHICKENPOX

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The etiologic similarity between herpes zoster and varicella has been noted for a long time. Von Bokay first suggested this in 1888, and since then many reports have upheld his original observations (1). There have been many accounts of varicelliform eruptions clinically indistinguishable from varicella following exposure to cases of herpes zoster (2, 3). The reverse of this, although uncommon, has also been reported (4). In a study by Bruisgard of 18 children inoculated with zoster vesicle fluid, eight developed lesions, four typical of zoster, and four typical of varicella (5).

Recently, Bereston and Robinson described the first case of zoster and varicella occurring in identical Negro twins after a single exposure to varicella virus (6). We would like to report a similar case occurring in siblings.

### CASE REPORT

A 1½ year old Puerto Rican female was brought to the emergency ward of The Mount Sinai Hospital with a vesicular eruption of the right frontal and molar areas of two days duration. There was contact with a case of chickenpox seven days before the onset of the eruption. Physical examination revealed a well nourished child with a temperature of 99.8°F. Over the right frontal and molar areas was a vesicular eruption on an erythematous base, typical of herpes zoster (Fig. 1). Three days later the eruption was more extensive and involved the right conjunctiva and iris. The temperature had risen to 101.4°. Fortunately, within ten days the eruption had subsided a great deal and eye involvement was minimal. The temperature returned to normal.

Seven days after the onset of the patient's lesions, a 2½ year old male sibling was brought to the emergency department with the classical history and physical findings of varicella. Inquiry revealed that there had been contact with the original case of varicella.

### DISCUSSION

A close antigenic relation between herpes zoster and varicella was established as far back as 1929 by River and Eldridge by neutralization, complement-fixation and agglutination tests. Electron microscopic studies in 1948 by Rake *et al.* showed viral bodies from vesicles of varicella and zoster are brick-shaped and identical in size (210–250  $m\mu$ ) and appearance. Roller tube cultures taken from both diseases have permitted critical analysis of antigens by complement-fixation, neutralization and fluorescent antibody tests (7). These tests strongly suggest the identity of the varicella and zoster viruses.

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The incubation period of varicella is well accepted as fourteen to twenty-one days. The incubation period of zoster, although difficult to establish is three to seven days (7). Since both children in our case came in contact with the same case of chickenpox, it is reasonable to assume that the two diseases were caused by the same virus. Why one child developed zoster and the other varicella is hard to explain but perhaps this is due to variations in immunological response. It is interesting that this occurred in the identical twins reported by Bereston and Robinson (6).

There is a remote possibility that the zoster may have been a reactivation of a latent earlier varicella infection or that the infection may have been due to an atypical virus. Considering the ages of the children the initial possibility is unlikely; since virology studies were not done, we cannot rule out the latter possibility.

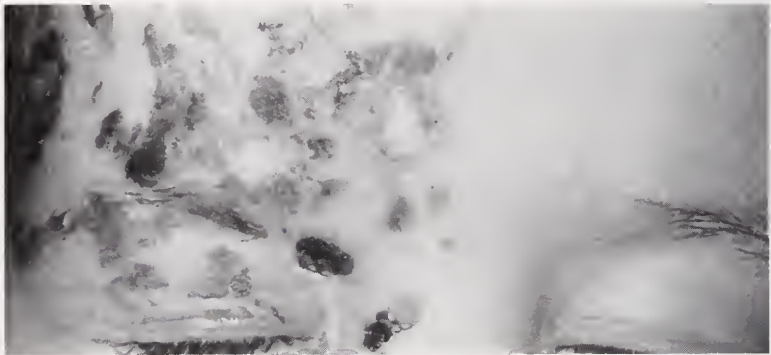


FIG. 1. Herpes zoster ophthalmicus in 18 month old child.

#### SUMMARY

A case of varicella and zoster occurring in siblings after a single contact with a case of varicella is reported.

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# *Clinico-Pathological Conference*

## HEPATIC AND RENAL FAILURE WITH ABNORMAL SERUM GAMMA GLOBULIN

*Edited by*

Fenton Schaffner, M.D.

A 72 year old Jewish Russian-born retired garment industry worker was admitted to The Mount Sinai Hospital for evaluation of anemia of nearly three years duration.

He had been relatively well until about three years prior to admission when he had a severe attack of bronchitis. He was hospitalized for this elsewhere and was treated with penicillin with a good response. At this time he was found to have anemia and hepatomegaly. Bone marrow was described as hyperplastic with increases in granulocytic cells and erythroblasts, and serum electrophoreses revealed an abnormal spike in the fast gamma region with otherwise normal gamma globulin. Questionable lytic lesions were seen on skull x-rays but no Bence-Jones protein was ever detected in the urine despite mild persistent albuminuria. He was given blood transfusions and discharged taking prednisone, 10-20 mg/day. No bleeding tendencies were ever present and follow-up x-rays failed to show progression of any bony lesions. During the ensuing year and a half, he continued to be anemic, hemoglobin dropping as low as 7.4 Gm, and required occasional blood transfusions. Hepatomegaly increased but the spleen was not felt. About twenty months after he was first hospitalized, transient jaundice was noted and thymol turbidity and cephalin flocculation were abnormal. Diarrhea and fever were also present. The spleen was felt for the first time. Barium enema showed diverticulitis of the colon and he was treated with sulfonamides to control his diarrhea. Bone marrow was reported as hyperplastic with an increase in normoblasts, erythroblasts and eosinophiles. Serum electrophoresis again showed a spike in the fast gamma region with decreased gamma globulin. During the year prior to his admission to this hospital, he received several transfusions and oral and parenteral hematinics because of low hemoglobin and weakness. He continued to take prednisone. He had frequent temperature elevations to 102° with no chills. Some ankle edema developed three months before he was hospitalized which responded quickly to chlorothiazide. About two weeks prior to admission, jaundice was again noted, this time accompanied by dark urine, pruritus, and anorexia. He then received two doses of urethane without demonstrable effect.

He passed a kidney stone 27 years earlier; 17 years earlier he was told he

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y. Presented on the occasion of a postgraduate course on "Recent Advances in Metabolic Diseases" of the American College of Physicians (1960).



had osteoarthritis in his right hip and arteriosclerosis of his right lower extremity. A finding of gallstones had been confirmed several times. He had varicose veins ligated six years earlier and at this time a mild normochromic, normocytic anemia was found, with a greatly elevated erythrocyte sedimentation rate, a trace of albuminuria and hyperproteinemia. His mother and father both died in their late eighties and two siblings died of infectious diseases as children. The patient denied excessive alcoholic intake, exposure to toxins or use of medicines other than those prescribed. He noted mild pain in his legs when walking, numbness in his right toes for a period of years, and had an erythematous rash on both feet. He lost twenty pounds in two years, mostly in the last three months.

On examination he appeared pale and chronically ill with evidence of recent weight loss. Temperature was 100° and other vital signs were normal. His skin was icteric, dry and warm. A rash was present on his feet and telangectasia were seen on his face. The sclerae were icteric. Soft discrete lymph nodes were felt in the cervical, axillary and inguinal regions. The lungs were clear and the heart was normal except for a soft grade II apical systolic murmur. The upper border of the liver was percussed at the 5th rib anteriorly and the lower edge was felt about 3 fingerbreadths below the costal margin. It was smooth, soft and not tender. The spleen also extended to 3 fingerbreadths below the costal margin and was firm and not tender. The prostate was enlarged and smooth. Motion of the right hip was severely limited. Slight edema was detected in both legs. Varicose veins were prominent bilaterally and no pulses were felt below the femorals. Vibratory sense was absent in the right toes. No other abnormal physical findings were recorded.

The results of some of the laboratory tests are summarized in Table I. The urine had a normal specific gravity with no sugar, Bence-Jones protein or cells. Serum calcium and phosphorus were normal; stool guaiac examinations were negative. Coombs test, febrile and cold agglutinins and LE preparations were negative. Bleeding and clotting time, platelet counts and capillary fragility were normal. Plasma fibrinogen was 165 mg%. Serum mucoproteins were 55.6 mg% and zinc sulfate turbidity was 14.7 units. Venous pressure was 120 mm H<sub>2</sub>O and Decholin circulation time was 20 sec. Electrocardiogram was normal. Serum creatinine, 3.1 mg% and uric acid 1.7 mg% shortly after admission, rose respectively to 4.6 mg% and 12.2 mg% shortly before death at which time the serum alpha amino nitrogen was 6.6 mg%. The bone marrow was cellular with erythroid hyperplasia, increased lymphocytes and eosinophiles and normal megakaryocytes. No tumor cells were seen. A Sia test was faintly positive. Paper electrophoresis showed a fast gamma spike and a smaller peak in the mid gamma zone, while on starch gel electrophoresis a low gamma was seen with a spike between the origin and slow alpha 2 globulin. Immunoelectrophoresis was considered characteristic of macroglobulins, and ultracentrifugal analysis showed 30 to 50 per cent of the globulins to have a sedimentation constant of 19 Svedberg units.

Various roentgenologic studies revealed old Legg-Perthes disease of the right hip, bone islands in the ilium, subcortical lucencies in both radii and ulnae.

extensive vascular calcification in the legs and pelvis, cholelithiasis, splenomegaly, good kidney function, benign prostate hypertrophy with calcification, a normal heart shadow, clear lung fields and a prominent left hilum.

The patient was treated with prednisone, neomycin, low protein diet, vitamin supplements, enemas, vitamin K, potassium chloride, intravenous glucose and fructose. Despite the extensive treatment he steadily became more jaundiced and

TABLE I  
*Laboratory Data*

	6 yrs. earlier	3 yrs. earlier	2 yrs. earlier	1 yr. earlier	Admis- sion	1st week	2nd week	3rd week
Urine blood chemical findings								
Albumin.....	tr.	—	4+	tr.	tr.	tr.	—	—
Bile.....	—	—	—	—	+	tr.	3+	—
Urobilinogen.....	—	—	—	—	—	1:160	1:20	—
Hemoglobin (Gm%).....	11.8	8.5	9.0	8.0	9.6	10.9	12.2	12.0
Hematocrit (%).....	—	—	—	—	—	34	33	41
WBC (/mm <sup>3</sup> ).....	6400	6600	7000	5000	6450	5600	5400	—
Sedimentation rate (mm/ hr.).....	66	—	—	135	140	—	—	—
Eosinophiles (%).....	—	7	6	12	8	2	—	—
BUN (mg%).....	29.1	—	—	—	34	25	38	104
CO <sub>2</sub> (mEq/l).....	—	—	—	—	—	23.3	24.6	17.4
Chlorides (mEq/l).....	—	—	—	—	—	95	100	92
Sodium (mEq/l).....	—	—	—	—	—	129	134	125
Potassium (mEq/l).....	—	—	—	—	—	5.2	5.4	7.9
Albumin (Gm%).....	5.6	—	4.1	2.7	2.2	2.3	2.6	—
Globulin (Gm%).....	3.0	—	3.6	3.2	4.8	4.5	3.8	—
Bilirubin (mg%).....	—	—	—	—	4.8	14.8	23.2	50.8
Cholesterol (mg%).....	—	—	—	86	85	140	175	185
Cholesterol esters (mg%).....	—	—	—	—	66	—	115	125
Alkaline phosphatase ( $\mu$ ).....	3.7 <sup>1</sup>	2.5 <sup>1</sup>	3.6 <sup>1</sup>	3.3	19.6 <sup>2</sup>	16.7 <sup>2</sup>	18.0 <sup>2</sup>	15.7 <sup>2</sup>
Ammonia (mc/ml).....	—	—	—	—	2.2	—	1.4	—
Transaminase (GOT) ( $\mu$ ).....	—	—	—	—	—	145	139	107
Cephalin flocculation.....	—	—	4+	4+	4+	—	3+	3+
Prothrombin time (sec.) (patient/control).....	—	—	—	—	—	15/2	14.5/12	17/13

<sup>1</sup> Bodansky units.

<sup>2</sup> King-Armstrong units.

cachectic. Edema increased and ascites and a flapping tremor were seen at the beginning of the third week in the hospital. Urinary output began to decrease at this time. He was given resins to lower serum potassium, and small doses of insulin. He was also treated with parenteral steroids. After one week of oliguria, his blood pressure which had been normal dropped following an episode of diarrhea. With vasopressor agents it was temporarily corrected but the patient became confused and somewhat irrational. He also began vomiting and hic-coughing. Fine rales were heard over both lung fields; the abdomen became dis-tended with increasing ascites. Right upper quadrant tenderness and guarding

were noted in the last hours of life. Pulse became weak and irregular and the patient expired after 21 days in the hospital.

*Dr. S. Howard Armstrong, Jr.\*:* The patient had a questionable lytic lesion three years before his final admission. The lytic lesions in his skull (even with a gamma 1 spike in electrophoresis) do not necessarily mean multiple myeloma; sometimes it is hard to tell lytic lesions from venous lakes. He had no bone pain or masses but he was beginning to suffer with anemia, and fever which was not always clearly explained. There were no episodes of nasal bleeding, bleeding from the gums or difficulty after dental extractions. Because of his asthenia and continued modest normochromic anemia, he was treated with many transfusions, and was given small amounts of prednisone. About a year and a half later, he had his first episode of jaundice and for the first time the spleen was felt.

When one has an original diagnosis of myeloma, one has to be very, very suspicious if splenomegaly is present. I have had to pay the house staff money because I once said at Cook County Hospital "You do not get a large spleen from multiple myeloma;" Dr. Popper confirmed the diagnosis. Nevertheless, splenomegaly in multiple myeloma is very unusual. On the other hand, in the condition perhaps most prominent in the differential diagnosis—Waldenström's syndrome—the occurrence of hepatosplenomegaly characterizes more than three-fourths of the existing reported cases.

The basic difference between Waldenström's syndrome and multiple myeloma relates to such matters as bone pain, which is absent in Waldenström's syndrome and very common in multiple myeloma, and bleeding phenomena which is much more common in Waldenström's syndrome than in myeloma. One can have hemorrhagic phenomena in myeloma, and it relates specifically to the ultracentrifugal findings of abnormal serum protein. Most of the abnormal serum protein is characterized by a sedimentation constant not too different from the normal serum gamma globulins, that is, about  $6\frac{1}{2}$  or 7 Svedberg units. In Waldenström's syndrome, however, there is a considerable amount of an abnormal serum protein of larger molecular size the sedimentation constant of which is usually between 17 and 20S and has in unusual instances been described as low as  $12\frac{1}{2}$  to 14S. The protein that characterizes Waldenström's syndrome is not always homogenous in the ultracentrifuge. It cannot be differentiated from myeloma protein on electrophoresis, nor is it immunochemically a completely distinct abnormal protein. If one makes an antiserum against Waldenström's syndrome serum, and absorbs that antiserum against normal serum proteins, there remains some precipitin left against the abnormal, high sedimentation rate protein. However, one cannot demonstrate this precipitin for all patients, and there are various immunological specificities within this group of proteins which characterize Waldenström's syndrome.

The cell present in Waldenström's syndrome is generally considered different from the standard myeloma cell, the plasma cell. Waldenström described a cytoplasmic-poor lymphocyte. If one studies the cases that have been reported since his original publication, one finds that this has not always been present

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even with other manifestations of macroglobulinemia. In the few descriptions of the histopathology of the liver in Waldenström's syndrome with hepatomegaly, there is little mention of Waldenström's specific type of lymphocyte engaged in an infiltrating reaction, so that we are not entirely sure why some patients with Waldenström's syndrome have hepatomegaly. (It should be said, just to make things more confusing, that Waldenström's syndrome has, both in the classic description and in subsequent case reports, a modest degree of generalized lymphadenopathy. This can occur with, but is in no sense characteristic of, myeloma.) These peculiar lymphocytes have been described in biopsies obtained in Waldenström's syndrome. I have treated only one case of Waldenström's syndrome, and was able to find such cells.

In the recent literature on the occurrence of fast sedimenting gamma globulins (range of roughly 15 through 20S), one can find a variety of diseases in which excessive activity of the reticuloendothelial system was present, such as lymphatic leukemia and occasionally lupus erythematosus. Usually in these instances the amount of high-sedimenting globulin is extremely small, 3 or 4 per cent of the total protein, a value close to the normal serum's macroglobulin content. We must ask ourselves when we come to the physical examination of the patient, whether we should consider one of these other diseases as the basis of his hepatosplenomegaly, with lymphadenopathy, or accept the syndrome which Waldenström originally described. This is the differential diagnosis until we come to his episode of icterus; therefore, it is easy to suspect that he had two episodes of infectious hepatitis following transfusions. Waldenström's syndrome is not associated with jaundice of a hepatocellular character.

When he was admitted to the hospital he had no ascites. He had a little anemia and a soft liver. As a result of laboratory data, hepatic coma was apparently feared since there was an effort to keep his intestine free of materials which can add to the development of hepatic coma. He was given neomycin, prednisone and a low protein diet. He was also given vitamin K for a modestly compromised prothrombin time, and glucose and fructose for calories; and yet under this treatment he became progressively more jaundiced and more comatose. He began to accumulate fluid in his abdomen, and his urine output decreased. His bone marrow did not on this occasion indicate much more than the prior descriptions of the bone marrow, except that it was specifically stated that there were no tumor cells present. His urine was interesting in that he was not at the end stage of "myeloma kidney," which patients with Waldenström's syndrome rarely develop, since the protein that they have is so large that it does not easily escape in the urine. His serum did not show any evidence of cold agglutinins, positive Coombs test, or cryoglobulins. It is of particular interest that he had no evidence of cryoglobulinemia since about one-fourth of the cases of Waldenström's syndrome have cryoglobulinemia; that is to say, a protein of high sedimentation constant, which when chilled, forms either a precipitate or a gel. This can result in a clinical triad of a bleeding tendency, Raynaud's phenomenon and thrombosis. It is important in the treatment as it has been shown that this high molecular weight protein when it has the ability to make a gel can be depolymerized *in vitro* and *in vivo* to a normal molecular weight. The first substance



tried clinically was penicillamine. Recently, it has been shown that if a patient who has symptoms related to cryoglobulinemia is given 10 million units of penicillin G, the serum viscosity can be reduced by a factor of ten in six hours. This large molecule, which is twelve times longer than it is wide, breaks up into molecules about the size of normal gamma globulins. If this treatment is continued with benemid and penicillin, the symptoms disappear. This will happen on penicillin G which is not a good therapeutic agent, and also on 0.5 Gm three times a day of penicillamine. I asked Dr. Popper if the treatment had been followed with this patient, and he said that it was not. Great enthusiasm has been claimed for this treatment but I do not see how it would improve a Waldenström's syndrome without cryoglobulinemia. I do not know whether in this type of Waldenström's syndrome the same depolymerization of an S-19 molecule can be induced, and if it is of value.

This was not his terminal problem; he went into an apparent hepatic coma with a flapping tremor. His oliguria proceeded to anuria and his blood pressure fell. At the end of his illness he also developed some right upper quadrant tenderness, which patients with Waldenström's syndrome should not have. Was there lurking in the background of this patient, who had many transfusions, something so common as a stone in the common duct with incomplete obstruction and infection ascending into his liver? I certainly would not interpret liver function tests with Dr. Hanger in the audience.

*Dr. Franklin M. Hanger\**: There is very little to add to this masterful discussion of Dr. Armstrong. I think we have all agreed that this could not be anything but a macroglobulinemia. He pointed out many of the insults to the liver that this patient had suffered. He had been exposed to hepatitis virus via transfusions. We know he had gallstones. Several other possibilities arise. We know that in amyloidosis, abnormal globulins, are sometimes deposited in the liver, thereby impairing hepatic function. Also, this patient had anemia, probably hemolytic, for a long time. He had many transfusions and, in addition, received iron parenterally. A liver cell filled with inorganic iron is a vulnerable cell and tends to die. But this man had a soft liver, which tends to rule out chronic hepatitis or unsuspected cirrhosis, hemosiderosis, or amyloidosis. I had hoped that Dr. Armstrong would tell you why this man's liver failed so rapidly. Several fantastic thoughts might be raised. Macroglobulins may show very peculiar surface affinities. Sometimes they cause a conglomeration of erythrocytes which may lead to hemolysis. The globulin of this patient did not adhere to the red blood cells because the Coombs test was negative but the question arises whether this protein which I would call "biological glue" can stick to other cells selectively, and affect their normal viability, adhering to their surfaces. I, too, have never heard of liver damage resulting from dysproteinemia in Waldenström's disease, but these cases differ from one another, and this may be the first one we have ever seen. After all, the number of documented cases is not very large. I think this man did die of hepatic insufficiency and would

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suggest that this dissolution of the liver was an acute episode superimposed on a chronic disease. Perhaps he had a thrombosis in his hepatic veins or even a tumor. One case in the literature did have a tumor of the liver, which apparently was one of the sources of the abnormal globulin. A small tumor at the point where the large vessels enter the liver, can compress the blood supply to the liver and cause widespread hepatocellular damage. I would hate to commit myself further. I think it will be extremely interesting if the pathologists can elucidate why this liver deteriorated so rapidly.

*Dr. Armstrong:* Before we turn the discussion over to Dr. Popper, I would like to see the radiologic evidence, or lack of it, for bone lesions, because the diagnosis of Waldenström's syndrome will be less conclusive if there are actual lesions present.

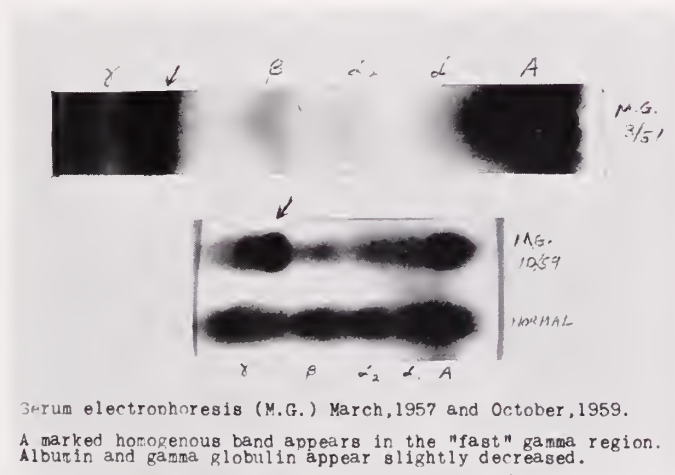


Fig. 1. Paper electrophoresis strips showing fast moving gamma globulin peak.

*Dr. Bernard S. Wolf\*:* There were no localized lytic lesions in the long bones. A quite diffuse process was absent in the fibula, the pelvis and the spine. In the skull no definite localized lytic lesions or evidence of myeloma was present.

*Dr. Armstrong:* I would like to discuss the electrophoretic and the ultracentrifugal diagrams. On paper electrophoresis in the gamma area, a very intense band was seen which is referred to either as the myeloma gamma I or as Waldenström's protein, which cannot be distinguished by electrophoresis alone (Fig. 1). In both of these syndromes the normal gamma globulin is very considerably reduced. On starch gel electrophoresis, an abnormal-band which was a very intense black area, was present in the front part of the gamma. Immuno-electrophoresis studies were not diagnostic of macroglobulinemia although a double immune component was seen in the gamma fraction. Some of the protein, which is characteristic of one of these immune components, was also found in

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the urine, which indicates that this material is not all of a molecular weight comparable to a sedimentation concentration of 19, and that there is dissociation of such materials *in vivo*. This may be a naturally dissociating system whose equilibrium is very much shifted (without exhibition of sulfhydryl drug) by differences between serum and urine. The ultracentrifugal diagnosis was made because of the presence of a serum abnormal component with a sedimentation constant of 19, and an abnormally small amount of S-7 gamma globulin.

I am glad Dr. Hanger was not willing to commit himself any further than I. I would like Dr. Popper to explain why this kidney deteriorated so suddenly. Dr. Hanger suggested para-amyloid. I wonder if in addition to the hepatorenal syndrome there was something in the vascular system that was indeed a para-amyloid factor. It does not appear to be a simple prerenal deviation. Therefore, my final diagnosis is the syndrome of Waldenström's macroglobulinemia, and, possibly, a serious problem relating to the biliary tract which none of us wants to define further. With the sudden appearance of ascites, a portal vein thrombosis is possible but unlikely, and finally, there is a factor in the kidney which I am unable to explain.

*Dr. Irving M. London\**: I would agree, as far as the underlying disease is concerned, that this man does have Waldenström's macroglobulinemia. The jaundice is very disturbing. The man did have gallstones, but because of the rapid progress of his jaundice and the appearance of ascites, I think that we have to rule out extrahepatic biliary obstruction, even if it were associated with bacterial infection. The man could have had a lymphosarcoma but I think the soft liver and the rapid demise are very much against that. Too little has been said about the episode of jaundice previously; it is unlikely that a man would have two attacks of viral hepatitis following transfusions. I think he had viral hepatitis, with apparent progression to postnecrotic cirrhosis.

*Dr. Hans Popper†*: We will now try to see whether we can answer the questions which the clinicians have posed for us. The bone marrow appeared red and when we looked at it histologically, we saw no destruction of the bone trabeculae. The bone marrow was cellular and we recognized a great variety of cells with circumscribed nodules, nodules in which a small cell of lymphocytic character with hardly any cytoplasm, the so-called protein lymphocyte, was prominent. This is related to protein synthesis, but for the morphologist it is somewhat difficult to understand that the cell with hardly any cytoplasm and, therefore, little ergastoplasm could form protein. However, we did see a large number of plasma cells. Therefore, we found in the bone marrow mainly a mixture of two types of cells, plasma cells and small lymphocytes or almost naked nuclei (1) (Fig. 2). The lymph nodes were enlarged in many places. They had a fleshy character in which the architecture was usually not recognized. A protein material was distributed between the monotonously appearing small lymphocytic cells (Fig. 3)

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which otherwise presented the appearance of a lymphosarcoma with invasion of the capsule (2). Under these circumstances we would call this lymphosarcoma. I have described two different features: 1) primarily lymphocytic and plasma cells in the bone marrow; and 2) lymphosarcoma in the lymph node with preservation of the architecture such as recognizable sinuses and connective tissue pattern only in places. The material deposited has been called "paraprotein," and is probably a combination of proteins with carbohydrates (Fig. 4).

As we studied the other organs, we saw lymphocytic infiltration in the adrenal, which clearly was lymphosarcoma. This was seen as well around the pancreas,

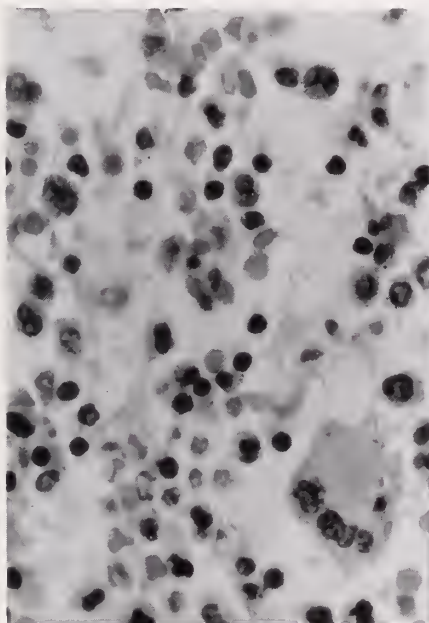


FIG. 2. Accumulation of small lymphocytes intermixed with plasma cells in bone marrow. (H & E  $\times 400$ )

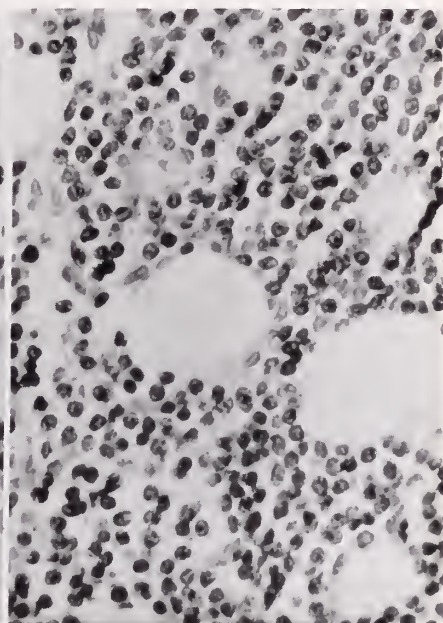


FIG. 3. Small lymphocytes in lymph node presenting picture of single cell type as in lymphosarcoma. (H & E  $\times 240$ )

the parathyroids and in the brain. Dr. Armstrong has asked me what we could demonstrate in the kidney. The kidneys were green as a result of biliary nephrosis, but biliary nephrosis does not lead to acute renal failure. There were also lymphoid infiltrations of the lymphosarcomatous type with some fibers between them. Again, this would not lead to renal failure. Looking further, we found a fairly large amount of fat in fine droplet form distributed on the bases of the epithelial cells. However, the most significant findings were: 1) deposition of a material which is clearly a carbohydrate-protein complex in many of the tubules, in places crystalline in character (Fig. 5); and 2) thickening of the glomerular membrane. This was in a sense a membranous glomerulitis without any cellularity. We suspected that this protein material was possibly



related to the macroglobulins and may not have left the kidney. This could be solved because we were fortunate enough to obtain from Dr. Osserman anti-19S globulin which was specifically bound to these protein deposits. This would prove that 19S proteins, extraneous to the kidney, could not pass and produced an obstruction. I was not satisfied with this explanation and have just learned that some investigators have been able to demonstrate cross-reaction between a 2S very small globulin and the 19S globulin by agar diffusion. I am not sure whether this demonstration was a cross-reaction with a small, broken-down type of macroglobulin, of which Dr. Armstrong has spoken, or the original 19S.

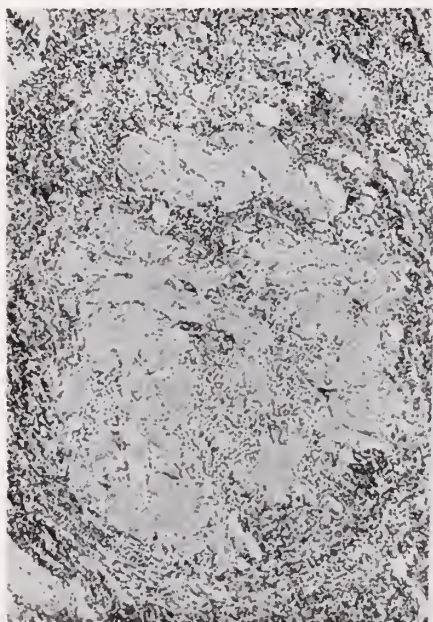


FIG. 4. Paraprotein deposit in lymph node. (H & E  $\times 120$ )

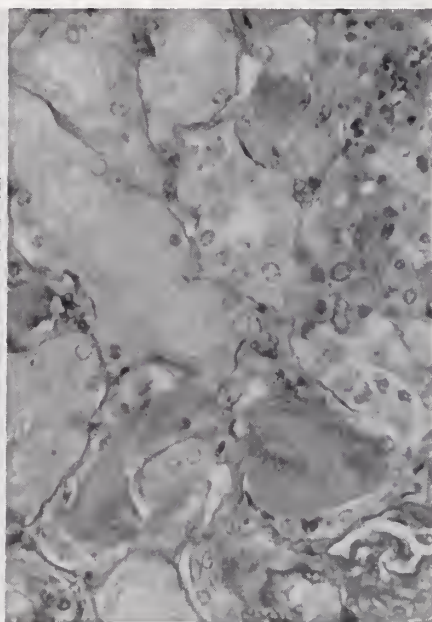


FIG. 5. Crystals and precipitate in proximal convoluted tubules and membranous glomerulitis without increase in cells. (PAS  $\times 400$ )

The heart was of normal size, and the only change of possible significance was edema between the heart muscle fibers and slight cellular infiltration, perhaps of the character of myocardosis, as has been described in the so-called dysproteinemias. The lungs show some indentations on the surface, but on microscopic examination there were some small peribronchial infiltrations. In and around the bronchi, accumulation of pus was noted and in the center of the pus a peculiar material, obviously fungal, was seen (Fig. 6). In the presence of a disturbed antibody formation with low normal gamma globulin and with steroid therapy, there was a monilial infection of the lung which I do not think contributed much to the demise of the patient. The inflammatory exudate contained a large number of plasma cells as well as lymphoid-appearing cells. In the

stomach we saw many areas of hemorrhage. This was not the only area in which hemorrhagic tendencies were noted but we were unable to find esophageal varices.

We were able to find the cause of terminal pain in the abdomen as we saw marked thickening of a small intestinal loop in a segmented area which was associated with inflammation and edema, and thickening was also seen in the colon. On microscopic examination, a leukocytic infiltration extended to all layers. The pain which had concerned our clinical discussants was obviously related to this terminal phlegmonous invasion of the intestine.

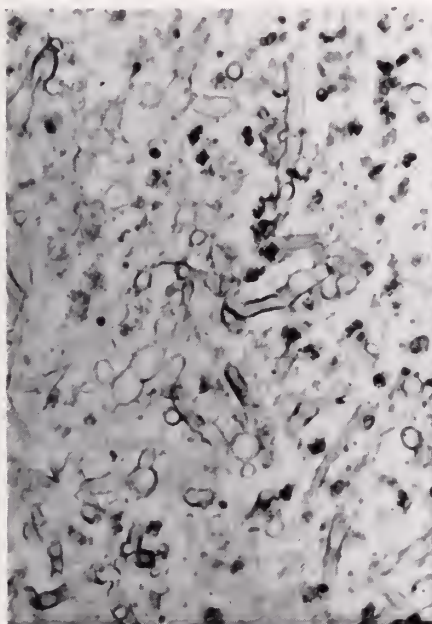


FIG. 6. Alveolar exudate containing fungus. (H & E  $\times 400$ )

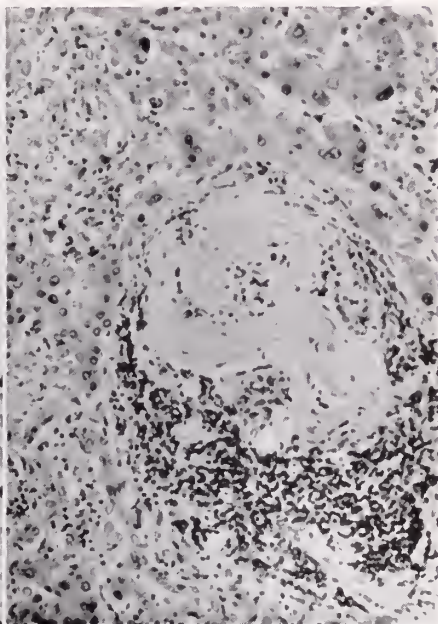


FIG. 7. Portal tract of liver with lymphocyte infiltration and para-protein deposition. (H & E  $\times 120$ )

The spleen weighed 500 Gm. Its architecture was preserved but somewhat altered. On the border of a rudimentary lymph follicle there were atypical cells and the picture was different from what we would expect in a small cell lymphosarcoma. It looked also like a "fibroadenia" or fiber formation in portal hypertension. The evidence of portal hypertension was not clear. Marked reticuloendothelial proliferation was present with many cells with a large amount of cytoplasm, reminding us of plasma cells, but apparently derivatives of the reticuloendothelium of the spleen. We, therefore, now had a third cellular element confusing us somewhat, namely, reticuloendothelial derivatives of what we would call plasma cells in addition to small lymphocytes and plasma cells (1-3). These cells were quite distinctly positive with pas stain but they were even more

distinctly positive with pyronine. This stain suggested protein formation and we wondered what this protein might be. We used the anti-macroglobulin and found it to be specifically in these cells and assumed it was produced there.

The last organ is the liver. It weighed almost 1400 Gm. Its architecture was a little bit obscured and it was somewhat green. Gallstones were present but they were rather small and appeared innocent. The common duct was not dilated and I do not think they produced obstruction nor did they cause what obviously was hepatic failure. At the hilum of the liver, no tumor was present. The histologic picture showed two components. One was severe portal and central in-

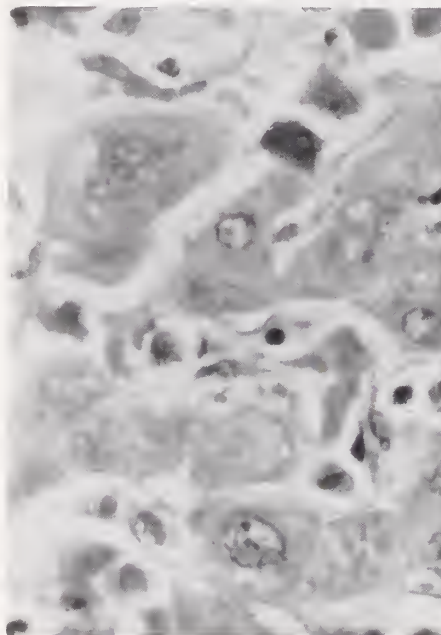


FIG. 8. Disintegration of liver cells with variation in size and shape of cells. (H & E  $\times 240$ )

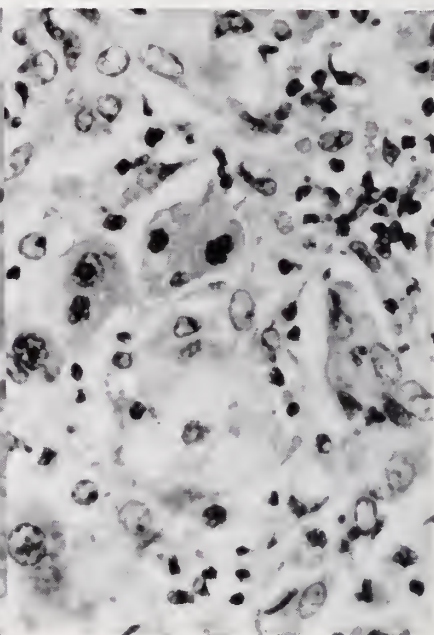


FIG. 9. Reticuloendothelial plasmacytoid cells in liver showing strongly positive PAS reaction. (PAS  $\times 450$ )

filtration with many small lymphocytes and paraprotein deposition (Fig. 7). There was also quite an extensive number of inflammatory cells as well as irregularly arranged liver cells. I had the benefit of reviewing the literature and I found three cases of cirrhosis which were said to occur in Waldenström's disease as a result of the dysproteinemia (3-5). However, I do not think cirrhosis was present in this case. The connective tissue of the portal tract was in no way increased. If there was an insult some time before, it apparently had not left any changes. In the hepatic parenchyma, we recognized focal necrosis of the liver cells with the accumulation of mononuclear cells. We also saw ballooning, fatty degeneration and proliferation of the liver cells (Fig. 8). Acidophilic bodies and areas of collapse where liver cells had disappeared, were noted. There was lipo-



fuscine and marked iron accumulation in the reticuloendothelial cells and in the liver cells. The patient did receive blood transfusions and Dr. Hanger thought that the iron contributed to the damage, which apparently it did not do. Severe bile stasis was also present. I believe this was viral hepatitis, modified by the cells of the Waldenström syndrome (3, 4). A large number of reticulum cells proliferated and extended into sinusoids; we never see this in viral hepatitis. These cells had a large amount of cytoplasm which stained with PAS (Fig. 9). All these cells were rich in nucleic acids suggesting protein formation. Staining for the 19S gamma globulin showed a very strong reaction. Our group has been interested in gamma globulin formation in liver diseases in general and characteristics of viral hepatitis and postnecrotic cirrhosis in which 7S gamma globulin appears in the liver. In this case only one cell was found in a section which means virtually no 7S gamma globulin. In an ordinary case of viral hepatitis such cells would be found in large numbers.

In summary, this was a reactive hyperplasia or, more probably, neoplasia with cells which could respond to inflammation in viral hepatitis. Three types of cells were present: lymphoid cells, plasma cells and reticulum cells. The organ manifestations were those of a transition between small cell lymphosarcoma, myeloma, and what we would call a reticulosis (3, 5, 6). The products of the cells were globulins, probably immunologic in nature. However, autonomous formation of protein can occur from tumor cells under the influence of an inflammatory reaction as, in this instance, viral hepatitis. Simultaneously, S7 gamma globulin formation was suppressed under these circumstances. At the same time, a tissue paraprotein formed, characteristic of the Waldenström syndrome. The destruction of the lymph node architecture was incomplete and leukemia, bone destruction or Bence-Jones urinary protein was not present.

The case we have before us has several elements of interest. First, the cellular infiltrations in the bone marrow resulted in anemia six years before and then produced lymphadenopathy, hepatomegaly and splenomegaly with renal endocrine and pancreatic involvement. Second, abnormal protein formation led to a high sedimentation rate, hemorrhagic tendency due to the presence of the very large globulins, and a myocarditis which explains the cardiac failure (7). There are several features that probably contribute to the renal failure: the dysproteinemia, which produces membranous glomerulitis, the large casts, and the fat which is characteristically found in cases of destruction of the liver as, for example, from viral hepatitis. The viral hepatitis a year before and again five weeks before death, accounts for the hepatic failure and ascites. In the presence of severe hepatitis, and possibly related to low gamma globulin, intestinal phlegmon occurred to produce peritonitis. The pulmonary fungus infection was only an added insult.

*Dr. Armstrong:* Dr. Popper, it is wonderful to see this type of pathology. In your sections of the kidney were you able to see the same amount of fluorescence in the glomeruli as you were in the tubules?

*Dr. Popper:* Only in the tubules.

*Dr. Armstrong:* It may be a question of quantity. Obviously, fluorescent reactions are quite dependent upon quantity.



*Dr. Alexander B. Gutman\**: In the course of the clinical studies here, we had come to conclusions similar to those of Dr. Armstrong and Dr. Hanger, who deserve our congratulations. I want to thank Dr. Henry G. Kunkel of the Rockefeller Institute who carried out the ultracentrifugal studies and Dr. Fred Osserman for the plates that he made. The material in the urine, the 2S compound, is the first that either Dr. Osserman or we have encountered in this disease. This is not a Bence-Jones protein. Its nature is not known. It is something new that we will have to look for in cases of macroglobulinemia. Dr. Osserman stated that this disease runs a protracted course and ends with tumorous formations which the pathologist is very apt to designate lymphosarcoma. It is precisely this sequence of events that occurred here and it is one with which we have become quite familiar in this hospital in the last year or two. The second and last point that I want to make is that the vulnerability to hepatitis virus in this patient may not have been altogether coincidental. We have learned that in idiopathic or acquired hypogammaglobulinemia seen in adults, demise with terminal hepatitis is by no means uncommon. We suspect that there was, as Dr. Popper indicated, a deficiency of immune body gamma globulins which, for reasons that are not altogether clear, made this patient more vulnerable to the hepatitis virus.

*Final diagnosis:* 1. WALDENSTRÖM'S MACROGLOBULINEMIA WITH WIDESPREAD HYPERPLASIA OF LYMPHOCYTES, PLASMA CELLS AND RETICULUM CELLS; 2. VIRAL HEPATITIS (PRESUMABLY SERUM HEPATITIS); 3. PHLEGMONOUS ENTEROCOLITIS; 4. HEMORRHAGIC GASTRITIS; 5. FUNGAL PNEUMONITIS (MONILIA); 6. MEMBRANOUS GLOMERULITIS.

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# *Radiological Notes*

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*New York, N. Y.*

## CASE NO. 143

This was the first admission of a 56 year old female with the chief complaint of "falling of the womb" for seven years. More recently, she developed dull lower abdominal pain and a pelvic mass was found. She did not complain of incontinence or frequency. Examination on admission was not remarkable ex-



Case 143, Fig. 1. Intravenous urography shows good concentration of the opaque material in both upper urinary tracts. There was no evidence of any dilatation or deformity of the pelvis or calyces on either side. Within and extending out from the lower pole of the right kidney (arrows), there is a soft tissue mass with calcific periphery 3 to 4 cm in diameter. The right superior aspect of the bladder shows extrinsic pressure and there is a suggestion of a soft tissue mass on the right side of the pelvis.

cept for the pelvic findings. There was a second degree prolapse of the uterus which was also retroverted. On the right side of the pelvis, a mass about three inches in diameter could be felt. Hemoglobin was 11.4 Gm, and white blood count 6,200 with a normal differential count. The urine was normal.

Intravenous pyelography (Fig. 1) showed an indentation on the right superior aspect of the bladder. An unexpected finding was the presence of a calcific ring outlining a mass related to the lower pole of the right kidney, 3 to 4 cm in maximum diameter. There was no deformity of the collecting system of either kidney or evidence of hydronephrosis. It was pointed out in the x-ray report that the mass in the right kidney need not be a cyst and might represent a solid tumor with peripheral calcification.

At exploration, hysterectomy and bilateral salpingo-oophorectomy were performed because of a tumor of the right ovary 8 cm in diameter. In the right kidney, a solid mass approximately 4 cm in diameter was found arising from the lower pole. A right nephrectomy was done. The pathological report was hypernephroma of the kidney with extensive necrosis and calcification, as well as a theca-cell tumor of the ovary.

This case is presented to illustrate the fact that ring-like peripheral calcification may occur in a solid tumor of the kidney. The assumption that such calcification is due to a benign cyst is likely to be incorrect. In most instances, in this country, calcification of this type is due to a hypernephroma. This has been recently emphasized by Cannon, Zanon and Karros (1).

*Case Report:* HYPERNEPHROMA OF THE KIDNEY SIMULATING A CALCIFIED CYST.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Arthur Davids and Dr. Murray Pincus.

#### REFERENCE

1. CANNON, A. H., ZANON, B., JR., AND KARROS, B. G.: Cystic Calcification in the Kidney. Its Occurrence in Malignant Renal Tumors. *Am. J. Roentgen. & Rad. Ther.*, 84: 837, 1960.

#### CASE NO. 144

This was the first admission of a 65 year old white male who five years previously had undergone abdomino-perineal resection for carcinoma of the rectum. The patient had done well until about six months prior to admission when he experienced recurrent pains in the left flank. These were not associated with chills or fever. Ten days prior to admission, he experienced intermittent gross painless hematuria and an intravenous pyelogram failed to show visualization of the left kidney.

On admission, physical examination was negative except for the presence of a colostomy on the left side. Hemoglobin was 9.8 Gm, wbc 5,000 with a normal differential count. The urine showed a moderate number of red cells and white cells. On cystoscopy, an impassible obstruction was found in the distal third of

the left ureter. Retrograde ureterography demonstrated complete obstruction to the retrograde flow of the opaque material (Fig. 1). At the site of obstruction, the ureteral lumen flared in a trumpet-like fashion and there was a sharply demarcated hemispherical filling defect. The soft tissue shadow of the left kidney



Case 144, Fig. 1. Retrograde opacification of the ureter shows complete obstruction to the retrograde flow of the opaque material in the distal third of the ureter. At this site, the ureter is symmetrically dilated in a trumpet-like fashion with a sharp distal arcuate margin of a globular filling defect (arrow). The left kidney is markedly enlarged with a lobulated contour. A row of metallic sutures is seen low on the left side as a result of previous abdomino-perineal resection.

appeared to be markedly enlarged and lobulated. The diagnosis of an intraluminal tumor in the ureter was made from the roentgen examination.

The patient was explored through the old scar and the distal portion of the left ureter exposed with considerable difficulty. The lower portion of the ureter was found to be of normal caliber. It was traced proximally where it was found to be surrounded by very dense fibrous tissue. Several sections of this



fibrous tissue were examined by frozen section and reported as showing simply chronic inflammatory reaction. The dense fibrous coat around the ureter was carefully dissected free, exposing a normal thin-walled ureter which contained within its lumen a soft mass. The ureter at this site was dilated in a bulbous fashion around the intraluminal mass. The further course of the ureter was then traced more proximally towards the kidney. During this dissection, because of the dense inflammatory reaction about it, an opening was made into the ureter and papillomatous type tumor extruded from the lumen. The distal  $\frac{2}{3}$  of the ureter were then excised down to the uretero-vesical junction. A left lumbar incision was made and a markedly hydronephrotic kidney resected with the proximal residual portion of the ureter. The patient did well postoperatively. Microscopic examination of the tumor within the distal ureter revealed adenocarcinoma. In addition, there were similar metastatic implants in the markedly dilated pelvis. It was concluded that these lesions represented metastases from the carcinoma of the rectum previously resected, not by direct extension but by lymphatic or vascular pathways.

*Case Report:* INTRALUMINAL METASTASIS TO THE URETER FIVE YEARS AFTER ABDOMINO-PERINEAL RESECTION FOR CARCINOMA OF THE RECTUM.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Stanley Glickman.

#### CASE NO. 145

This was the second admission of a 52 year old male who seven years previously had undergone subtotal gastrectomy for a mucous-cell carcinoma of the stomach. No involved nodes were present. The patient had no complaints until one year prior to this admission when he developed intermittent right lumbar pain. During this period, he lost twenty pounds in weight. Intravenous pyelography showed hydronephrosis on the right. The patient was admitted for further investigation.

On admission, physical examination was noncontributory. The urine contained many white cells. Hemoglobin was 10.4 Gm, wbc 11,000 with 88 per cent polymorphonuclear leucocytes. Right retrograde ureteropyelogram (Fig. 1) showed a rat-tail type of constriction in the distal third of the ureter over a distance of  $1\frac{1}{2}$  to 2 inches. The ureter proximal to this site was moderately dilated as was the visualized portion of the collecting system of the right kidney. Obstruction was incomplete. Exploration of the region of the right ureter was performed and revealed markedly indurated retroperitoneal tissue surrounding the lower third of the right ureter, infiltrating its wall. Ureterostomy and drainage were performed with removal of periureteral tissue. The pathological report was metastatic adenocarcinoma invading the lymphatics and retroperitoneal nodes. Shortly postoperatively, a rectal shelf became palpable.

This case is presented as another example of metastatic neoplasm involving



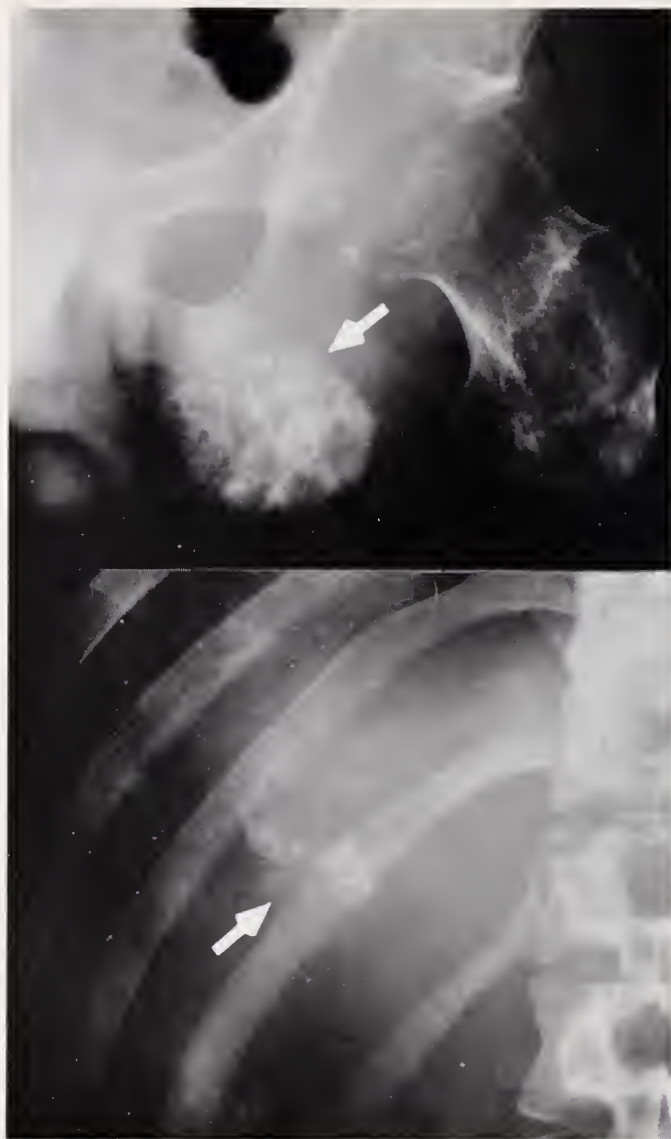
Case 145, Fig. 1. Retrograde ureteropyelogram shows a rat-tail narrowing (arrow) of the distal third of the ureter immediately proximal to the uretero-vesical junction extending over a distance of  $1\frac{1}{2}$  to 2 inches. Obstruction is incomplete. The ureter proximal to the lesion is moderately dilated. The filled calyces in the upper pole of the right kidney are rather markedly dilated. Opaque clips in the left upper quadrant indicate the site of anastomosis at the previous subtotal gastrectomy.

the ureter. In contrast to the previous case, however, involvement of the ureter is clearly by direct extension from the retroperitoneal tissues.

*Case Report:* METASTATIC CARCINOMA OF THE URETER; PRIMARY IN THE STOMACH.

#### CASE NO. 146

This was the first admission to this hospital of a 23 year old male who six months previously had undergone a left leg amputation for an osteogenic sarcoma. He was admitted because of severe dyspnea, fever, cough, weakness and anorexia. Examination on admission showed a markedly dyspneic chronically ill male with severe cyanosis. There was evidence of a pleural effusion on



Case 146, Fig. 1. Examination of the pelvis shows the left femoral stump which is markedly osteoporotic. In the region of the femoral triangle (arrow), there is an ovoid mass about  $2\frac{1}{2}$  inches in maximum diameter containing irregular trabeculated new bone.

Case 146, Fig. 2. Examination of the upper abdomen shows within the liver shadow (arrow) a less discrete area of ossification. The presence of a pleural effusion on the right obscures the diaphragm.

both sides, more marked on the right. In addition to the findings in the chest, there was tenderness and guarding in the right upper quadrant and the lower edge of the liver extended 3 to 4 fingerbreadths below the costal margin. Hemoglobin was 9 Gm; white blood count was not elevated.

Roentgen examination of the chest confirmed the presence of a large right pleural effusion with numerous metastatic lesions in both lungs. Examination of the pelvis including the residual portion of the upper end of the left femur showed severe osteoporosis. In addition, however, a large ovoid mass (Fig. 1) with diffuse ossification was seen in the soft tissues in the region of the femoral triangle. This clearly represented metastatic nodes occupied by osteogenic sarcoma. Examination of the abdomen (Fig. 2) showed a somewhat similar but poorly demarcated area of ossification apparently located within the liver. The patient's general condition was markedly improved as a result of pleural taps, chemotherapy and radiotherapy.

This case is presented because of the rather unusual findings of ossification in osteogenic sarcoma metastases to lymph nodes and to the liver.

*Case Report:* OSSIFICATION WITHIN LYMPH NODES AND LIVER DUE TO METASTATIC OSTEOGENIC SARCOMA.

#### CASE NO. 147

This patient was first admitted to this hospital at the age of five, in 1952, with a history of intermittent colicky abdominal pain for about two and a half years. One year prior to admission, the child had been admitted elsewhere because of jaundice which cleared rapidly. Episodes of abdominal pain persisted, however, and jaundice reappeared shortly prior to admission. On this first admission, the liver appeared to be enlarged. The spleen was not palpable, jaundice was moderately severe, and liver function tests indicated obstructive jaundice without parenchymal damage. The jaundice gradually subsided over a period of two to three weeks. Oral cholecystography was attempted but showed no visualization. The significance of this was not clear since the patient was recovering from jaundice. It was decided to discharge the patient and observe her for a further period of time. The child did quite well for the next three years but again developed right upper quadrant pain, nausea and vomiting and was admitted to the hospital a second time for further investigation.

On admission, the child complained of severe abdominal pain but was afebrile and white blood count was normal. Hemoglobin was 10.5 Gm. There was marked tenderness and spasm of the abdominal wall particularly in the right upper quadrant. The day after admission, the sclerae became icteric but jaundice disappeared in several days. The abdominal signs also subsided within 48 hours. Because of the suspicion of a congenital anomaly of the biliary tree, the patient was explored through an incision in the right upper quadrant. The surface of the liver was smooth. The gall bladder was moderately distended with some thickening of its wall. The common bile duct was exposed and was markedly dilated, about an inch in diameter, with marked thickening of its wall. The common



bile duct was opened and a large amount of muddy bile removed by suction. The openings of the hepatic and cystic ducts could be visualized and did not appear to be dilated. The first portion of the duodenum was in close proximity to the common bile duct and there was no difficulty in performing a choledochoduodenostomy. Biopsy of the liver was also done and subsequently reported as normal, with no evidence of obstruction or inflammation.



Case 147, Fig. 1A. Intravenous cholangiography and tomography show good visualization of the gall bladder (arrow A) which does not appear to be remarkable. Immediately medial to it, at the site of the common duct, there is a cyst-like dilatation (arrow B) about an inch and a half in its transverse diameter which contains at least a half dozen lucent filling defects. There is an abrupt transition between the cyst and the more proximal moderately dilated biliary radicles.

Postoperatively the child did extremely well. She was readmitted about one year after the second admission because of acute appendicitis with abscess formation. An acute gangrenous appendix was removed and the abscess drained without subsequent complication.

The patient had few or no complaints until recently (about five years after the anastomotic procedure). Now, there are times when she complains of mild right upper quadrant discomfort. Because of this, intravenous cholangiography was performed with rather surprising findings. There was good concentration of

the opaque material in the biliary tree (Fig. 1A). The gall bladder itself did not appear to be remarkable. In the region of the common duct, however, there was a large sac about  $1\frac{1}{2}$  inch in its transverse diameter which contained at least a half dozen ovoid calculi. The biliary radicles proximal to the common



Case 147, Fig. 1B. Thirty minutes after a fatty meal, the gall bladder has contracted satisfactorily. Gas has entered the choledochal cyst. The opaque material demonstrates the communication (arrow) between the cyst and the duodenum. Most of the opaque material has left the cyst and the biliary radicles.

duct were moderately dilated. The cystic duct was not clearly visualized but presumably was normal. Thirty minutes after administration of a fatty meal (Fig. 1B), the gall bladder was normally contracted and the anastomosis between the common duct and the duodenum was clearly demonstrated. Gas appeared in the cyst and biliary tree as the opaque material emptied into the duodenum. Another film (Fig. 1C) of the right upper quadrant taken about an

hour after the administration of a fatty meal showed complete evacuation of the opaque material from the gall bladder and the duct system. The calculi within the dilated common duct could be visualized by contrast with the contained gas. Since the patient had no serious complaints and was doing well clinically, a further period of observation was recommended.

The patient is of interest because of the demonstration of the results of



Case 147, Fig. 1C. Re-examination of the right upper quadrant one hour after the administration of a fatty meal shows complete emptying of the gall bladder and of the cyst and biliary radicles. A considerable quantity of gas is now present in the biliary tree. The calculi are evident as filling defects within the gas column. The choledochal cyst (arrow) has contracted to some degree but is still at least an inch in its transverse diameter.

choledochoduodenostomy for a choledochal cyst. Despite the fact that the anastomosis appears to be functioning quite well, she has developed numerous calculi in the cyst. These are clearly a potential source of trouble and sometime in the future will have to be dealt with by reoperation.

*Case Report:* CHOLEDOCHAL CYST, CHOLEDOCHODUODENOSTOMY, AND SUBSEQUENT APPEARANCE OF COMMON DUCT STONES.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Ernest Arnheim.

## CASE NO 148

A 17 year old boy was admitted with a history of periumbilical pain of four days duration which had increased in severity within the previous twenty-four hours. The pain was associated with low grade fever but no vomiting, nausea, anorexia, constipation or diarrhea. Examination on admission showed deep tenderness in the region of the umbilicus with questionable rebound tenderness throughout the abdomen referred to the umbilicus. Temperature was 99.8, hemoglobin was 13 Gm, wbc 9,700 with 71 per cent polymorphonuclear leukocytes. The impression was acute appendicitis. Exploratory laparotomy was promptly performed through a right McBurney incision. There was a small amount of serous fluid within the peritoneal cavity. The lymph nodes in the small bowel mesentery were enlarged. The appendix was retrocecal in location but, when exposed, was normal in appearance. The distal four feet of the small bowel, when delivered into the wound and inspected did not appear to be abnormal. There was no Meckel's diverticulum. A prophylactic appendectomy was performed. The postoperative impression was "mesenteric adenitis." The pathological report on the removed appendix was "appendix showing carcinoid." The carcinoid was small and an incidental finding. The immediate postoperative course did not appear to be eventful and the patient was discharged in five days. However, shortly after discharge, the patient complained of periumbilical pain which radiated to the left lower quadrant and became persistent. Temperature was elevated to 101 degrees. The boy was readmitted five days after discharge. Examination showed the abdomen to be somewhat distended with deep tenderness on the lower left side of the abdomen somewhat greater than in the umbilical region. In the left lower quadrant, there was slight rebound tenderness as well. The remainder of the physical examination was not remarkable. Hemoglobin was 10 Gm, white blood count 16,800 with 68 per cent polymorphonuclear leukocytes including 22 per cent band forms. Stool was guaiac 4+ on two occasions. Sedimentation time was moderately elevated. Additional investigations included intravenous pyelogram and barium enema which were not contributory. G.I. series and small bowel examination were then done. These showed evidence of a soft tissue mass just to the left of the midline in the lower abdomen, around which a poorly filled loop of small bowel appeared to be adherent (Figs. 1A, 1B). A definite intrinsic lesion of the small bowel was not demonstrated. Because of the findings on the small bowel series and the physical findings pointing to the same area, the possibility of an inflammatory mass was considered. However, the possibility of a neoplasm, presumably a lymphoma, was also suggested. The abdomen was re-explored through a left paramedian incision. In the lower jejunum, a tumor mass about 7 cm in length involving one wall of the bowel was found. The lymph nodes in the adjacent portion of the mesentery were markedly enlarged and edematous and formed a conglomerate mass. These continued as a chain involving almost the entire root of the small bowel mesentery. Complete resection of the mass in the small bowel with the adjacent enlarged lymph nodes was considered impossible because it would have entailed removal of the entire superior mesenteric artery and its branches. Since the patient had evi-



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Case 148, Figs. 1A and 1B.

dence of gastrointestinal bleeding, it was deemed advisable to perform a palliative resection of the small bowel tumor. This was done and an end-to-end anastomosis performed. The segment of small intestine removed was about 5 inches in length. On the mucosal aspect, a flat firm nodular growth about 2½ inches in length was noted with superficial scattered ulceration and hemorrhagic spots. The wall, however, throughout its thickness was thickened in a completely encircling fashion for a distance of about 1½ inches. A section of the wall showed white and gray indurated tissue which extended from mucosa to serosa. Histological examination was reported as "lymphosarcoma with acute inflammation and ulceration." A small lymph node attached to the mesentery also showed early lymphosarcomatous change.

The immediate postoperative course of this patient was satisfactory and he was transferred elsewhere for further therapy.

This case is presented because of the confusing clinical picture and the minimal roentgen findings. The most prominent feature at exploration was the presence of enlarged nodes. These at first were mistaken for mesenteric adenitis because they appeared to be acutely swollen and inflammatory.

*Case Report:* LYMPHOSARCOMA OF THE SMALL BOWEL AND MESENTERY WITH ACUTE INFLAMMATION SIMULATING MESENTERIC ADENITIS.

#### ACKNOWLEDGMENTS

This case is presented through the courtesy of Dr. Samuel DeLange and Dr. Gerson Lesnick.

#### CASE NO. 149

This was the first admission of a 78 year old white male with the chief complaint of weight loss for one year and "colitis" for 17 years. Diarrhea began explosively but was never bloody. He claimed that in the intervening years he had had diarrhea daily but was able to carry on his activities without difficulty. For a period of about a year and a half prior to admission, he had received cortisone with some improvement in his diarrhea. In a period of several months prior to admission, he had experienced several episodes of vomiting soon after eating and he had lost at least 15 pounds. Examination on admission showed a rather cachectic looking, elderly male who appeared chronically ill. There was no peripheral adenopathy. The abdomen was slightly distended. Temperature was normal. Hemoglobin was 15 Gm. WBC was 8,900 with a normal differential count. The stool on multiple occasions was guaiac negative. Sigmoidoscopy and barium enema examination were not contributory. Barium meal

Case 148, Fig. 1A. Barium meal examination shows a poorly filled loop of small bowel (arrow A) which appears to be closely applied to the outer medial aspect of a soft tissue mass. Additional evidence of an extrinsic mass is displacement of adjacent loops (arrow B).

Case 148, Fig. 1B. Later in the examination, the soft tissue mass is demonstrated by compression of adjacent gas-filled loops of bowel (arrows).

examination was done and showed almost complete obstruction in the distal jejunum (Fig. 1). At the site of obstruction, the bowel appeared to be markedly angulated and details at the site of angulation could not be clearly delineated.



Case 149, Fig. 1. Film from the small bowel examination shows practically complete obstruction in the jejunum. The jejunum proximal to this site is markedly dilated. There appears to be rather marked angulation at the site of obstruction with such small amounts of barium passing that details of the nature of the lesion could not be determined. The correct diagnosis of lymphosarcoma was not suspected because of the marked obstruction present. Obstruction of this type is very unusual in lymphosarcoma of the small bowel. (Incidentally, there are changes of Paget's disease in the right side of the pelvis.)

The patient was then treated for small bowel obstruction by intubation and suction and supportive measures and operated upon within a week after the barium meal examination. About four feet from the ligament of Treitz, an an-

nular obstructing lesion was found with no evidence of enlarged lymph nodes. No other lesions were detected in the small bowel and an examination of the colon was also negative. A segmental resection of the small bowel was performed. The specimen removed was about a foot in length. Approximately in its center, there was a slightly elevated, moderately indurated tumor mass about 3.5 cm in longitudinal diameter, completely encircling the bowel wall. The edge of the tumor was sharply demarcated from the normal bowel. The mucosa over the tumor was somewhat eroded. The serosal aspect of the tumor showed multiple small nodules, grayish-white in color. A cross section of the wall showed that the tumor completely replaced the wall. The cut surface was very wet and cellular. Microscopic examination was reported as showing a solitary ulcerated lymphosarcoma.

Postoperatively, the patient did well and was discharged in two weeks. However, he had to be readmitted ten months later because of recurrent small bowel obstruction. At re-exploration, the region of the previous anastomosis was intact and there was no evidence of recurrence at that site. However, tumor mass was found in the pelvis involving a loop of ileum and adjacent lymph nodes. A second tumor about 5 cm in diameter in the ileum was resected but a large number of involved nodes had to be left behind. This tumor was reported as necrotic lymphosarcoma with marked ulceration. Subsequent to this second operation, the patient received radiotherapy and chemotherapy and did fairly well for a period of about two years. He died as a result of massive hemorrhage into the gastrointestinal tract.

This case is presented because the correct diagnosis of lymphosarcoma of the small bowel was not suspected preoperatively. This was true not only of the clinicians but also in regard to the roentgen interpretation. Up to the present time, we have seen only two examples of essentially complete obstruction of the small bowel due to lymphosarcoma (in the absence of intussusception) and the case presented is one of these.

*Case Report:* CONSTRICTING LYMPHOSARCOMA OF THE JEJUNUM WITH INTESTINAL OBSTRUCTION.



# *Abstracts*

## *Papers Presented before the Research Club of The Mount Sinai Hospital New York, N. Y.*

*Electron Microscopic Studies of Diabetic Nephropathy*, Willy Mautner, M.D., Edith Grishman, M.D., and Jacob Churg, M. D. (Department of Pathology and Cell Research Laboratory) Supported by Research Grant A-918 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U.S.P.H.S.

Renal biopsies of seven cases of diabetes mellitus, including four with the nephrotic syndrome, were studied by light and electron microscopy. Six of these cases had the so-called "diffuse" type of intercapillary glomerulosclerosis; three in addition, showed the "nodular" Kimmelstiel-Wilson lesion.

Glomerular capillary basement membrane alterations were found in all of these cases, including one case in which the only manifestation of diabetes was a diabetic glucose tolerance curve and in which there was no clinical evidence of nephropathy. Two types of changes could be distinguished electron microscopically: 1) diffuse thickening of basement membranes with retention of homogeneity and of smooth inner and outer border; 2) markedly irregular thickening of the basement membrane with scalloped outlines, especially on the epithelial side, and marked variation in density, resembling the picture of "membranous glomerulonephritis." Subendothelial electron-dense deposits were also found in some cases.

Six of these cases also showed marked proliferation and thickening of the intercapillary basement membrane branches with consequent enlargement of the intercapillary spaces. In cases with nodular lesions, this proliferation and thickening proceeded to an extreme degree with obliteration of the intercapillary cells.

It is suggested that the "diffuse" lesion of diabetic nephropathy consists of both a generalized intercapillary sclerosis and diffuse basement membrane changes, and that the nodular lesion represents an extreme progression of the diffuse intercapillary alteration.

*Radiologic Localization of the Esophageal Hiatus Determined by Intraesophageal Pressure Measurements*, Bernard R. Cohen, M.D., and Bernard S. Wolf, M.D. (Department of Radiology.)

The level of the esophageal hiatus can be readily recognized on intraluminal pressure measurements by identification of the point of pressure inversion (P.I.P.) with respiration. The "pinchcock action" on a column of barium in the esophagogastric region has been used roentgenologically to identify the level of the hiatus. In deep inspiration, the column of barium is interrupted, *i.e.* an "empty" segment is produced with the formation of a saccular structure ("phrenic ampulla") situated above the "empty segment." It has been assumed that the junction of the phrenic ampulla with the empty segment represents the

level of the hiatus. This, however, has been questioned. An attempt was therefore made to correlate the roentgen features with manometric localization of the hiatus.

In this study, P.I.P. in deep inspiration was determined by securing six catheters in the esophagus. The openings in these catheters, marked by radio-paque clips, were spaced at 1.0 cm or 0.5 cm intervals and located so as to straddle the esophogastric area (method to be described). In seven subjects, P.I.P. was recorded simultaneously with the taking of a film in deep inspiration. In eleven additional subjects, P.I.P. was determined before and after taking of an inspiratory film. Within the limits of the method, estimated to be  $\pm 2$  mm, identical localization of the physiologic hiatus (P.I.P.) and the distal end of the phrenic ampulla was uniformly demonstrated.

*Effects of Hypothermia and Extracorporeal Circulation in Experimental Myocardial Infarction with Shock.* Leslie A. Kuhn, M.D., Frank Weiser, M. D., John D'Aria, M.D., A. Robert Beck, M.D., and Irwin Krasna, M.D. (Department of Medicine.)

Prolonged hypothermia was induced in 43 dogs following plastic sphere coronary embolization. In twenty blood-stream cooled animals ventricular fibrillation (VF) occurred at an average esophageal temperature of 20.8C and arrest at 12C. In eight maintained by extracorporeal circulation at 5 to 10C for five hours, prolonged VF occurred but defibrillation on rewarming was successful in all. Of the 14 kept at 28–30C for 4 to 5 hours, there was no arrhythmia. One of 11 skin-cooled dogs maintained at 28 to 30C fibrillated.

Cardiac output (CO), mean central aortic pressure (MAP) and left ventricular contractile force (LVCF) diminished following embolization and systemic vascular resistance (SVR) increased slightly. In the blood-stream cooled animals, CO, MAP and LV work diminished progressively with increasing hypothermia. SVR and LVCF increased. LV diastolic and RA pressures were unchanged. Skin-cooled dogs maintained at 28–30C did not manifest a similar fall in CO, LV work or a rise in SVR. Hypothermic animals demonstrated return to or near pre-embolic CO, MAP, SVR and LVCF following rewarming. In contrast, six dogs remaining normothermic for similar periods following embolization demonstrated no rise in CO or MAP.

It is concluded that a dog with acute coronary embolization and shock is not more sensitive to hypothermic arrhythmia than a normal animal and that there is little irreversible deleterious hemodynamic effect after five hours of profound or moderate hypothermia combined with extracorporeal circulation. Animals rendered hypothermic following embolization demonstrate, on rewarming, more adequate recovery of MAP, CO and SVR than do those remaining normothermic for similar periods.

*Isolation of a Neutral Protein-Carbohydrate Complex from Native Canine Gastric Mucus.* Martin I. Horowitz, Ph.D., and Franklin Hollander, Ph.D. (Gastrointestinal Physiology Research Laboratory.)

Macromolecules containing hexosamines are an integral part of all mucinous secretions, and investigation of the structure of such macromolecules is an important prerequisite to an understanding of the viscous character of mucus. Anacid gastric mucus, obtained by topical application of acetylcholine to the mucosa of dogs' Heidehain stomach pouches, was separated into fluid and gel fractions by centrifugation. Previous investigation revealed the presence of serum proteins in both of these fractions. The present investigation is directed at the isolation and characterization of hexosamine-rich components of the gel fraction.

The gel was homogenized in borate buffer (pH 9.0). Fractional ethanolic precipitation of the homogenate gave a precipitate at 50–60% EtOH which contained the major part of the hexosamine. Further increase in hexosamine content of this fraction was effected by sequential treatment with carboxymethylcellulose at pH 5.1 and diethylaminoethylcellulose at pH 8.8. This procedure consistently gave large amounts of unadsorbed protein and hexosamine. A protein-carbohydrate complex was obtained from this fraction by precipitation in 60% EtOH (pH 7.0). The molar ratio of nitrogen to hexosamine was 11.6:1, and of reducing power to hexosamine was 2:1. Only negligible amounts of sialic acid and hexuronic acid could be detected, but a significant amount of fucose was present. The isolated complex behaved as a neutral entity on paper electrophoresis. Methods for determining its homogeneity are currently being investigated. It is possible that application of this procedure or of a refinement of it will lead to the isolation of a pure gastric mucin in a state of minimum degradation.

*Further Observations on Reflex Effects of Intra-arterial Injection of Hypertonic Saline in Dogs.* Richard Lasser, M.D., Douglas Allen, M.D., Myron R. Schoenfeld M.D., and Charles K. Friedberg, M.D. (Division of Cardiology, Department of Medicine.)

Previously reported studies have demonstrated that hypertension and tachycardia can be reflexly provoked by rapid injection into a peripheral artery of hypertonic saline and dextrose (1.4 to 10× hypertonic). Current observations demonstrate that the central synapse lies in or below the medulla, since the reflex is not abolished by brain transection at the medullopontine junction. Constant intra-arterial (femoral) infusion of 0.9% and 2.5% saline, 2 cc per minute for 20 minutes was administered to 10 dogs anesthetized with tubocurarine 4 units/kg and sodium pentobarbital, 5 mg/kg. Average rise of systemic arterial pressure in 12 trials of 2.5% saline was 24–21 mm Hg range 21–49/17–52 mm Hg without change in heart rate. No responses were obtained to similar intravenous (femoral) infusion or with 0.9% saline intra-arterially. Intra-arterial infusion of 2 cc of 2.5% saline per minute (0.86 mEq per minute) can be estimated to raise local arterial Na concentration 10 to 20 mEq/L considering blood flow at 100 cc per minute. Determination of plasma Na in simultaneously drawn femoral vein specimens from infused and opposite limbs in 7 dogs revealed the former to be 7 mEq/L higher than the latter. It is believed therefore

that the osmo-circulatory reflex is activated by alteration in Na concentration within conceivable physiologic variation.

*Enhanced Calcium and Phosphate Excretion Following Intrarenal Arterial Injection of Digitalis Glycosides.* Jonah D. Kosovsky, M.D., and Sherman Kupfer, M.D. (Department of Medicine.) Supported by a grant from U.S.P.H.S., H-4845.

Utilizing the Bartram technique, anesthetized isotonic saline loaded dogs (80-100 cc/kg I.V.) were prepared so that the individual GFRs, and the excretory rates of Na, K, Cl, Ca, Mg and phosphate could be sequentially followed. Strophanthin kombe or digoxin (0.05-0.1 mg/kg) was very slowly injected into one renal artery. Within 75 to 120 minutes following the injection, a significant ipsilateral diuresis and increase in the excretory rates of the above ions were consistently observed which could not be related to changes in renal hemodynamics. The relative increments in the excretory rates of both calcium and phosphate at the height of the drug action approximated 25 per cent or more of the filtered loads, exceeding that for sodium. This selective pattern of ion excretion was not observed when comparable rates of urine flow and sodium excretion were induced by a systemically administered osmotic or mercurial diuretic. These digitalis glycosides therefore affect active tubular ionic transport processes in a different manner and/or site(s) than either osmotic or mercurial diuretics.

*Fine Structure of Glomerular Capillaries in Proteinuria.* Jacob Churg, M.D., Willy Mautner, M.D., Edith Grishman, M.D., and Gilbert Eisner, M.D. (Department of Pathology and Cell Research Laboratory.) Supported by a research grant (A-918) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U.S.P.H.S.

Ninety-five renal biopsies in diseases associated with proteinuria were studied by light and electron microscopy. The walls of the glomerular capillaries showed a variety of changes, affecting the three layers (epithelium, basement membrane, endothelium) singly or in combination, and frequently accompanied by protein deposits. The epithelial cells (podocytes) showed the well-known fusion of foot processes, and also loss of the dark "foot-process material," swelling of the cytoplasm and accumulation of "hyaline" (protein) droplets. In some instances, the podocytes and their foot processes appeared entirely unchanged. The endothelial cells showed bleb formation and various degrees of edema. The basement membrane looked normal in some instances, but more often it revealed thickening, mottling, vacuolation, alternating "tooth-comb" thickening and thinning ("membranous transformation"), splitting into two or more parallel layers and stretches of marked attenuation. In a rare case, an otherwise normal membrane contained deep notches or defects. "Membranous transformation" was most often seen in nephrotic syndrome, either "idiopathic" or in the course of subacute glomerulonephritis, systemic lupus erythematosus or diabetes, as well as experimental antikidney serum nephritis. Fibrillar deposits were observed in amyloidosis and granular deposits in toxemia of preg-



nancy, diabetes, lupus and acute glomerulonephritis. In lupus the deposits sometimes extended from endothelium to the epithelium causing a break in the basement membrane. In acute glomerulonephritis the deposits were located between the basement membrane and the podocytes, and to a lesser extent within the basement membrane. In a case of chronic nephrotic glomerulonephritis splitting of the basement membrane was associated with extensive deposits between and around the split layers.

Relation of the capillary alterations to the proteinuria, the nephrotic syndrome and "membranous" glomerulonephritis is under consideration.

*A New Method for the Bio-Assay of Appetite Suppressants.* Gerald Friedman, M.D., Ph.D., L. A. Weingarten, M.D., and Henry D. Janowitz, M.D. (Division of Gastroenterology, Department of Medicine.)

At present, appetite suppressing drugs designed for obese patients are screened in normal animals. In addition, available animal assay methods lack the uniformity necessary for adequate quantification. The present study was designed to overcome these limitations by using hyperphagic mice made obese by aurothioglucose ("regulatory obesity"). The method provides: (1) a simple unique means of screening compounds with regard to appetite suppression in obese and nonobese animals; (2) an index for correlating central nervous system responses (locomotor activity) with appetite suppression; (3) a method for evaluating "tachyphylaxis" of sympathomimetic amines and (4) a means of testing cumulative or delayed effects of appetite suppressants.

Aurothioglucose obese mice and litter-mate nonobese mice were trained to consume their daily food intake in an eight hour period. Obese animals ate thirty per cent more food per day than controls. Following an adequate control period, daily graded doses (based on the estimated lean body mass) of various appetite suppressants were administered for four to five day periods and food intake compared with the corresponding control period. One week rest intervals allowed the animals to return to their previous levels of food intake and weight. Activity patterns (locomotor activity) were determined five to ten minutes following the subcutaneous administration of medication.

Dextro-amphetamine (5 mg/Kg) was employed as the standard and depressed food intake 23% in control animals and 30% in aurothioglucose obese mice, with four plus locomotor activity patterns. DL amphetamine produced similar food intake suppression and activity patterns at a dose of 10 mg/Kg, while phendimetrazine produced equivalent results at 15 mg/Kg. Diethylpropion was ineffective in these dose ranges. In general, appetite suppressant effects were paralleled by increased locomotor activity. The relative doses employed correlate well with results of double blind studies in human obese subjects.

*Usefulness of Single Lesion Infection in Experimental Amoebiasis.* Svetozar Teodorovic, M.D., (Department of Microbiology.) Supported by U.S.P.H.S. Grant E3283 (C1).

A new method has been developed by which a single lesion infection is established. The previous methods used in experimental amoebiasis did not pro-

duce well controlled infection with *Endamoeba histolytica* in experimental animals and it was impossible to standardize lesion or lesions. Therefore, those methods were not suitable for critical studies of many important problems such as: accurate evaluation of amebicides, early pathology of amebic lesion and histochemical study of the mechanism of tissue invasion by *Endamoeba histolytica*. Our method of intramural inoculation enables us to evaluate these factors.

*Description of the method:* Trophozoites or cysts of *Endamoeba histolytica* are inoculated subserosally into the wall of the cecum of the experimental animal. Thus, using only a minimum number of organism, producing negligible injury in the intestinal wall by using an inoculating needle of the smallest gauge (#27), a typical amebic abscess is established within the intestinal wall, which is for all practical purposes a sterile environment. Using the minimum volume of inoculum (0.1 ml) and choosing adequate location in the cecum wall, the lesion is standardized as far as to size, pathological characteristics, and perforation of the mucous membrane.

*Early pathology of amebic lesions:* Animals are sacrificed at regular intervals starting from two hours after infection and up to seven days. The lesion is described as far as the gross pathology is concerned from the serosa as well as from the mucosa side. The tissue is preserved and sections are prepared. The histological description of the lesion is given. The reactions from the surrounding tissue are analyzed.

*Evaluation of the amebicides:* Animals inoculated intramurally with *E. histolytica* are treated with the typical representatives of several groups of known amebicides and their amebicidal activity is expressed numerically, based on the standard value of the lesion.

*Effect of corticosteroids and tranquilizers on amebic lesions:* The animals inoculated intramurally are treated for several days with several corticosteroids and tranquilizing drugs and the inflammatory reactions in the tissues surrounding the lesion as well as the lesion itself are analyzed macroscopically and microscopically.

*Preliminary histochemical study of amebic lesion:* Animals intramurally infected with *E. histolytica* are sacrificed at various intervals, starting at four hours after inoculation and the tissue at the spot of inoculum is excised while the animal is still alive (anesthetized) and treated histochemically as far as the certain enzymes are concerned, as well as the other histochemical reactions.

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## PATTERNS OF BONE CHANGE IN MULTIPLE MYELOMA

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The term multiple myeloma, first proposed by Rustisky in 1873, is used to designate a lethal disorder of the reticuloendothelial system characterized by a neoplastic proliferation of plasma cells which vary in morphology and degree of maturity (myeloma cells). When this proliferation is generalized the condition is perhaps better referred to as myelomatosis. When there is a localized neoplastic proliferation of plasma cells the term plasmacytoma is more appropriate. Plasmacytomas may be single or multiple. In most cases of multiple myeloma, however, both generalized myelomatosis and multiple plasmacytomas are present.

The diffuse proliferation of plasma cells and their peculiar ability to produce certain proteins, notably globulins, leads to a great variety of abnormalities which make multiple myeloma a disease of considerable clinical interest, protean in its manifestations and sometimes difficult to diagnose.

Uncontrolled proliferation of myeloma cells in the bone marrow may result in bony abnormalities which are demonstrable radiographically. This continued cellular overgrowth impinges upon the normal centers of erythrocyte, granulocyte and megakaryocyte formation in the marrow, reducing them in number and leading to various degrees of anemia, leukopenia and thrombocytopenia. The anemia, when present, is of the normochromic, normocytic variety and may range from mild to severe. Almost invariably there is marked rouleaux formation in blood smears. This is not pathognomonic but when observed should strongly suggest the possibility of myelomatosis. There is usually a leukopenia, although in some cases the presence of numerous plasmaocytes in the peripheral blood (plasma-cell leukemia) results in a leukocytosis. The reduction in the marrow megakaryocytes results in thrombocytopenia, but this is only partially responsible for the hemorrhagic disturbances which are common in this disease.

## SERUM PROTEIN ABNORMALITIES

It seems reasonably well established now, that plasmaocytes contain a peculiar type of secretory cytoplasm which produces protein and that the extraordinary proliferation of plasmaocytes in multiple myeloma is responsible for the hyperproteinemia found in most cases. In this condition the total serum proteins may show an increase up to 10 grams or more per cent (1). In 91 cases studied by Reiner and Stern (2) the average value was 8.97 grams per cent.

The increase in serum protein is due solely to an increase in the serum globulins. The serum albumin is either low or normal. In recent years, the application of paper electrophoresis to the analysis of serum proteins in multiple myeloma has indicated that the hyperglobulinemia is due in most cases to increases in the

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gamma or beta globulins. The extent to which alpha globulin is responsible for hyperglobulinemia in some cases is still controversial. Gutman, *et al.* (3) have described as characteristic an "M" protein, with an electrophoretic mobility intermediate between that of beta and gamma globulin. Wintrobe and Buell (4) and others have found a cryoglobulin (*i.e.*, a globulin which precipitates at low temperatures) in some cases. This is not a common finding, however. Snapper, *et al.* (5) were able to find cryoglobulinemia in only one of 17 cases in which it was sought. When present it is usually associated with a hemorrhagic tendency and purpuric skin lesions. The latter are mainly localized to parts of the body exposed to cold.

Hyperglobulinemia is found in about sixty per cent of myeloma patients. One of the direct consequences of this increased serum globulin is the clumping together of groups of red cells into large aggregates with a resulting elevation of the sedimentation rate and the massing of red cells into aggregates of rouleaux which can be observed in blood and bone marrow smears.

The production of increased globulins is apparently of a pathological variety. The large amounts of abnormal gamma globulin appear to seriously interfere with the production of normal gamma globulin antibody and as a result lead to increased susceptibility to infections, especially pneumonia.

The excretion of Bence-Jones protein in the urine is an unique characteristic of multiple myeloma. Snapper (5) considers it to be practically pathognomonic. About 40 to 45 per cent of all cases of multiple myeloma show Bence-Jones proteinuria when tested by the specific reaction to heat and then cooling. According to Dameshek and Gunz (1), 75 per cent of cases have shown this abnormality when tested by immunologic methods. The relationship between Bence-Jones protein excreted in the urine and the abnormal serum proteins of multiple myeloma has not yet been determined. Bence-Jones proteinuria occurs more commonly in the absence of hyperglobulinemia and the reason for this inverse relationship is still not clear.

Apparently as a result of the increase in serum globulins, the formation of Bence-Jones protein and the increased viscosity of the blood, abnormalities in renal tubular filtration occur. Eventually there is cast formation, proteinuria and uremia. A significant finding in these cases is the usual absence of hypertension, even in the presence of severe uremia. Snapper, *et al.* (5) have emphasized this and called attention to its diagnostic implications. Geschiekter and Copeland (6) found that 86 per cent of the cases they studied showed evidence of "nephritis" at postmortem examination. Sixty-one per cent of these were associated with Bence-Jones proteinuria.

Amyloidosis is sometimes found in multiple myeloma and its occurrence in this disease is presumed to be related in some way to the production of abnormal globulins by the plasmaocytes. Snapper, *et al.* (5) found eight cases of amyloidosis in 41 cases of multiple myeloma studied at autopsy.

#### BONE LESIONS IN MULTIPLE MYELOMA

In a certain number of cases of multiple myeloma there may be no radiographically demonstrable bone changes whatsoever. Heiser and Schwartzman

(7) were unable to demonstrate any bone alterations in 6 of 62 cases (13 per cent). Snapper, *et al.* (5) found that in five of their 97 cases (5 per cent) there were no demonstrable bone lesions.

Osserman (8) using routine serum protein electrophoresis has presented evidence which supports the impression that radiographically evident disease is usually disease which has already progressed to an advanced stage. Some patients exhibit severe anemia, renal insufficiency, para-amyloidosis or manifestations secondary to cryoglobulinemia as the predominant feature of their clinical picture. Such patients may eventually develop significant skeletal changes, but some of them may pursue a clinical course resulting in death without ever having developed appreciable skeletal alterations. The application of serum and urinary protein electrophoresis in cases of unexplained anemia, unexplained increases in the erythrocyte sedimentation rate or unexplained proteinuria may be expected, in the future, to identify greater numbers of cases of myelomatosis before bone changes are demonstrable.

While none of the bone changes which may occur in multiple myeloma are pathognomonic of the condition, *certain patterns and localizations of bone involvement may be very strongly suggestive*, especially when occurring in patients over the age of forty. In the light of our present knowledge, however, some modification of former concepts of the roentgen appearance of multiple myeloma must be made. In current practice, cases of myeloma are seen for diagnosis at earlier stages than in the past and one must be prepared to suggest the diagnosis on far less skeletal change than the older text books describe. Formerly it was considered that the most common appearance of multiple myeloma in bone was that of multiple discrete or "punched out" areas of bone destruction more or less uniformly distributed throughout most of the skeleton and particularly in the skull. Review of large series of more recent cases indicates that the "punched out" lytic lesions are much less common than previously considered and that more commonly, *the tendency is for the skeleton to be involved by a combination of different lesional features*. Furthermore, while skeletal involvement may be diffuse in some cases, *the lesions of myeloma may be sparsely distributed in a few bones* and may, in fact, be limited to a lytic defect in a single bone. Actually, there is a relatively good correlation between the degree and extent of bone change and the duration of the disease. The skull, often used as the "clincher" when other skeletal lesions suggesting myeloma are found, is *not* always involved. *Even in cases where other portions of the skeleton are severely involved the skull may show no abnormality*.

Several authors have provided classifications for the roentgen bone changes which may occur in multiple myeloma (9-11). The classification suggested by Heiser and Schwartzman (7), with a few modifications, is adequate for descriptive purposes.

### 1. Osteoporosis

When involvement of the bone marrow is diffuse without the formation of discrete tumor foci, myeloma tissue encroaches upon adjacent bone, thinning the cortices and reducing the trabeculae in number and thickness. The result is

an increased lucency of the bone as seen radiographically. The skeleton may show a pattern of slight or advanced generalized osteoporosis but this type of bone alteration is predominant in the spine, particularly in the lower dorsal and



FIG. 1. Myelomatous Osteoporosis: There is a uniform partial trabecular absorption with cortical thinning but no vertebral collapse. The only other bone changes were an exaggeration of the reticular osseous pattern in the outer clavicles, the acromions, axillary borders of the scapulas and in the humeri. The skull was normal. The patient was a 55 year old female whose chief complaint was bone pain in the upper arms and legs.

lumbar regions (Fig. 1). In the spine, the appearance may range from moderate demineralization to increased degrees of lucency with cupping of the weakened vertebrae and compression fractures (Fig. 2). Occasionally, the vertebral trabeculae will be diminished but coarsened leading to a honeycombed appearance. *Multiple circumscribed osteolytic foci in the vertebrae are unusual.* Vertebral



FIG. 2. Myelomatous Osteoporosis: There is more irregular and more extensive absorption of the trabeculae with residual trabecular coarsening. The bodies of D<sub>12</sub> and L<sub>2</sub> are partially collapsed. Several vertebrae show cupping with expansion of the intervertebral disc spaces. The skull, pelvis, ribs and proximal extremities showed scattered areas of circumscribed osteolysis in porotic bone. The patient was a 56 year old female whose chief complaint was backache.



collapse is frequent. Heiser and Schwartzman (7) found vertebral collapse in 73 per cent of 51 cases in which the spine was examined. When present, vertebral collapse tends to be multiple but only occasionally is there collapse of contiguous vertebrae.

Jacobson, *et al.* (12) have been impressed by the frequency of relatively early involvement of the vertebral pedicles in metastatic carcinoma compared to preservation of the pedicles until late in the course of multiple myeloma. They have referred to this as the "pedicle sign." They found pedicle involvement in 94 per cent of 74 cases of metastatic carcinoma of the vertebrae and in only 15 per cent of 54 cases of vertebral myeloma. These authors relate the relatively low incidence of pedicular involvement in myeloma to the paucity of red marrow in the pedicles compared with much of the rest of the vertebra. Involvement of the pedicles in metastatic carcinoma, on the other hand, is due to embolization of tumor cells.

Vertebral involvement may also be accompanied by paravertebral soft tissue mass formation. While such formation is not common it may help, when present, to differentiate myeloma from metastatic carcinoma in which paraspinal soft tissue masses are more unusual.

*Generalized osteoporosis or osteoporosis limited to the central segments of the skeleton is often the sole roentgen manifestation of multiple myeloma.* On occasion only the spine may show demineralization. Since the chief complaint of many patients with multiple myeloma is back pain, the finding of a demineralized vertebral column may be the first clue to the diagnosis. Such a finding, however, requires differentiation from similar changes which may occur in postmenopausal and senile osteoporosis, hyperparathyroidism and other metabolic and hematologic bone diseases. One step in such a differentiation is a roentgen skeletal survey.

## 2. Sharply Circumscribed Destruction

Multiple sharply circumscribed areas of osteolysis are considered to be characteristic of multiple myeloma. When seen in patients over forty they are highly suggestive of myeloma but they are not pathognomonic. The variation in the size of such lesions is considerable.

Lesions of this type occur most frequently in the skull and long bones. They are often seen in other bones, however, with the exception of the vertebrae where their occurrence is uncommon. The lesions tend to be round and sharply margined with no surrounding bone reaction. On occasion, however, *there may be a thin border of increased density.* The trabeculae within the lytic area are completely effaced. Such lytic lesions may encroach upon the cortex and expand the bone, or may erode the cortex from within producing a sharply scalloped appearance (Figs. 3, 4). With progression there is invasion of the periosteum and adjacent soft tissues with formation of a soft tissue mass.

Rarely is there any periosteal reaction. Yentis (13), however, has recently described three cases in which there was new bone spiculation in multiple myeloma. This appeared as radial striae perpendicular to the lytic lesion and oc-



FIG. 3. Classical punched-out lesions of multiple myeloma. The rounded lytic areas are sharply margined and in some areas encroach on the inner surface of the cortex. There is generalized porosis of the bone. Note that several of the lesions have borders of increased density.

curred at the elbow, sternum and skull. The formation of soft tissues masses, on the other hand, is characteristic of myeloma and when present helps to differentiate this condition from metastatic carcinoma. Frequently, myelomatous in-



FIG. 4. Classical punched-out lesions of multiple myeloma. Encroachment on the inner aspect of the femoral cortex has resulted in scalloping. Coalescence of multiple lytic deposits in the ischium has resulted in an area of severe destruction which is the site of pathological fracture. There is generalized osteoporosis.

volvement of the ribs is accompanied by large subpleural nodular masses which at first may be mistaken for pleural or pulmonary lesions (Fig. 5). Not infrequently, they may be mistaken for metastatic carcinoma of the lungs. Actually, palpable tumors may result from expansion of the involved bone or from perforation of the cortex and extension into the soft tissue. We have found the ribs, ilium, clavicle and sternum to be the most common sites of palpable tumor formation. The femur and humerus may occasionally be similarly involved.

In the skull, the area most frequently involved by sharply circumscribed destruction, the lesions may be limited to a few small areas of lysis (Fig. 6), or the bone may be riddled with destructive lesions (Fig. 7). Figure 8 shows the marked variation in the size which these lesions may attain in the skull. In



FIG. 5. Myelomatous involvement of the ribs in a 56 year old male. The seventh left rib has been destroyed posteriorly. The involved portion of the rib is expanded and there is a hazy soft tissue density adjacent to the area of destruction. The lateral and anterior segments of the eighth left rib have been completely destroyed and the myelomatous tissue has formed a large soft tissue mass which resembles pleural scalloping. There is also diffuse destruction and widening of the posterior portion of the third right rib. Note also that small areas of lysis can be seen at the outer ends of both clavicles. In addition, there were scattered small areas of sharply circumscribed lysis in the skull and a large area of severe bone destruction in the left ilium.

some instances large areas of destruction may resemble osteoporosis circumscripta of Paget's disease. As the disease progresses small lytic lesions tend to coalesce to form large areas of destruction.

In the extremities, sharply circumscribed lytic lesions may be considerable in number or limited to a few sparsely distributed lesions or a single lytic defect (Figs. 3, 9, 10). Generally, there is an associated osteoporosis but often the adjacent bone is quite normal. In the lower extremities there is an interesting



tendency in some cases for the fibula to be involved, sometimes diffusely, while the tibia shows minimal or no changes (Fig. 11). In the radius, the lesions may be confined to or usually predominate in the region of the tuberosity.

When lytic lesions are found in the proximal humerus, they are apt also to be seen in the scapula along its axillary border and in the outer end of the clavicle (Fig. 12). *We have been impressed, in fact, by the frequency of involvement of the outer end of the clavicle and acromion even when the humerus and*



FIG. 6. Minimal multiple myeloma of the skull in a 58 year old male. There are a few small scattered circumscribed lytic areas in the frontal bone, along the coronal suture and probably in the posterior parietal region. The cranial bones are normally mineralized. Sparse small clearly defined lytic lesions of this type may be extremely difficult to differentiate from aberrantly placed paccchionian bodies. The fact that paccchionian bodies are usually parasagittal and communicate with vascular channels may be of no assistance in a given case since they may show marked variability in size, shape and position. The rest of the skeleton was riddled by areas of circumscribed osteolysis. The second and third lumbar vertebrae were collapsed. Six months after this film was made the skull was diffusely involved.

the remaining portions of the scapula are uninvolved (Fig. 13). Myeloma patients with large amounts of abnormal gamma globulins are apt to have lowered resistance to infection and recurrent pneumonias are relatively common. In older people, careful inspection of the clavicles on chest films taken for pulmonary disease may occasionally provide a clue to the diagnosis before the clinician's suspicions are aroused (Figs. 5, 14).

In the ribs, lytic lesions, sharply or poorly circumscribed, commonly expand the bone and pathological fracture is frequent, much more frequent, in fact, than in metastatic carcinoma. In myeloma, fractures are most common in the spine and ribs but also occur in the sternum, clavicles and long bones, especially

when the smaller lesions coalesce to form larger areas of destruction. Geschickter and Copeland (6) found pathological fractures in 62 per cent of their patients. Heiser and Schwartzman (7) found fractures in 70 per cent of 62 cases and Snapper, *et al.* (5) encountered fractures in 62 per cent of their 97 patients.

### 3. Poorly Circumscribed Bone Destruction

Unlike the often described sharply punched-out lesions characteristic of myeloma, lytic lesions may not be sharply margined and may gradually merge with the adjacent normal or osteoporotic bone (Fig. 15). Such lesions occurring



Fig. 7. Diffuse myelomatous involvement of the skull in a 46 year old female. The skull is riddled by multiple small punched-out areas of osteolysis. There were scattered circumscribed lytic areas in the ribs and femora but the bones were normally mineralized.

in the distal skeleton may simulate the destructive lesions of rheumatoid arthritis or gout (Fig. 16). Occasionally a solitary myeloma may begin as a poorly circumscribed area of bone destruction.

### 4. Severe Bone Destruction

There may be areas of complete replacement of bone by tumor producing homogeneously lucent lesions usually of considerable size. In our experience, this type of lesion has been relatively common in the sacrum where it is frequently easy to overlook because of overlapping or adjacent gas shadows (Fig. 17). Areas of severe bone destruction also commonly occur in the ilium and ischium (Fig. 18). Such lesions may occur in the sacrum or ilium as the only manifestation of myeloma or may be associated with a few scattered lesions in the skeleton or with diffuse bone involvement. Sacral lesions may be seen not

infrequently in examinations of the lumbosacral spine made to investigate the cause of low back pain. Severe bone destruction, when involving the spine, gives the appearance of very severe osteoporosis. Sometimes even the cortical shell is obliterated. In some cases, a large area of severe bone destruction is criss-crossed by large condensed trabeculae, resulting in a bizarre reticular pattern or a soap bubble appearance (Figs. 19, 20). Reticulated and soap bubble lesions



FIG. 8. Myelomatous involvement of the skull giving rise to scattered clearly defined lytic lesions of various sizes. The largest lesion is presumably the result of coalescence of multiple smaller areas of destruction. The remaining skeleton showed a pathological fracture of one rib and osteoporosis of the spine with multiple vertebral compression fractures. The other bones showed no evidence of myelomatosis and were normally mineralized.

are most apt to be found in the ilium or in a rib, but may be seen elsewhere (Fig. 21). When such lesions are solitary they may be mistaken for giant-cell tumor but it should be remembered that giant-cell tumors tend to appear in patients usually between twenty and forty years of age while myelomas only rarely occur before the age of forty. Furthermore, giant-cell tumors are rela-

FIG. 9. There are two small rounded circumscribed areas of osteolysis in the region of the left radial tuberosity. The surrounding bone is of normal density. There were sparsely scattered lytic lesions in the skull. The spine was osteoporotic and showed an area of destruction in the third lumbar vertebra. The remaining bones were uninvolved.

FIG. 10. A single punched-out lytic lesion which encroaches on the cortex of the upper femur.



FIG. 9



FIG. 10





FIG. 11. Diffuse myelomatous involvement of the right fibula by coalescent areas of destruction. The tibia is uninvolved. The left lower leg showed similar changes.



FIG. 12. There are multiple areas of circumscribed osteolysis involving the humerus, the axillary border and acromion process of the scapula. Small lesions are also present at the outer end of the clavicle.

tively uncommon in flat bones and are not as often trabeculated as is popularly supposed.

#### *5. Honeycombing*

A not infrequent pattern of bone change in multiple myeloma is that of diffuse destruction honeycombed by surviving trabeculae. When mild, this type of le-

sion can be easily missed since a less diffuse and less exaggerated similar pattern may be seen in normal bone (Fig. 22). Lesions of this type are most often



FIG. 13. Myelomatous involvement of the acromion and the outer end of the clavicle without involvement of the humerus and remaining portions of the scapula.

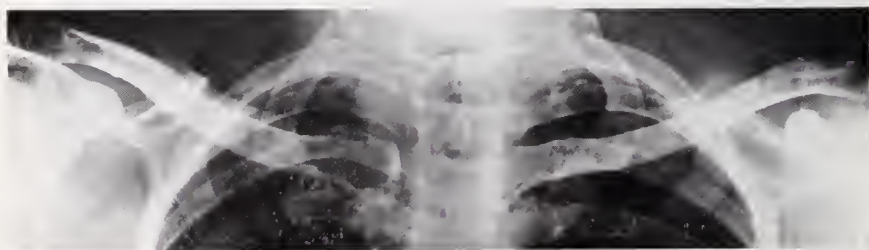


FIG. 14. There are sharply circumscribed areas of destruction in the outer ends of both clavicles. This is a frequent site of involvement by myeloma and is often associated with soft tissue mass formation and bone widening. The right acromion is also seen to be involved.

seen in the long bones but may involve the pelvis, especially the pubis and ischium and the ribs.

#### 6. Indeterminate

In some cases, the pattern of involved bone appears to be transitional between osteoporosis and poorly defined destruction. The pattern is essentially that of

diffuse demineralization within which are very poorly defined focal areas of osteolysis (Fig. 23). In many instances, one cannot be sure after careful study whether there are actually any discrete areas of lysis or whether the whole process is one of generalized demineralization. In such cases, serial examinations



FIG. 15. Poorly circumscribed area of bone destruction in 52 year old female. The lower margin of the defect merges with the adjacent normal bone. There is slight scalloping of the inner surface of the cortex. All other bones of the extremities were normal but there was an area of severe bone destruction in the sacrum and a single small well-defined area of lysis in the skull.

FIG. 16. There are multiple areas of both sharply and poorly circumscribed destruction involving the distal radius and ulna, the carpal bones and the proximal metacarpals. On occasion areas of poorly defined lysis at the wrist and in the feet may simulate rheumatoid arthritis or gout.

will show progression of the malignant lesions to recognizable areas of bone destruction.

### 7. Osteosclerosis

While myelomatosis typically provokes no bone reaction several cases of bone sclerosis in this disease have been reported (14-17). Three patterns have been described. In one, there are focal areas of sclerosis similar in appearance to metastatic carcinoma of the prostate. In another, perpendicular spicules of





FIG. 17. Severe bone destruction in myeloma. There is a large poorly defined area of homogeneous lucency in the left sacrum. While the lesion is not distinctive, the site is a common one for myeloma. This is the patient described in Fig. 15. She was examined because of low back pain. Lesions of this type, at this site, frequently present as single plasmacytomas which may exist for some time before roentgen evidence of generalized myelomatosis is demonstrable.



FIG. 18. There is an area of severe bone destruction in the ischium of a 40 year old male. The involved bone is expanded and there is slight scalloping of the inner aspect of the eroded cortex. There is also a large rounded area of osteolysis in the intertrochanteric portion of the femur. Note that this lesion has a dense periphery. These lesions and others in the sacrum, ilium and ribs were preceded by a single plasmacytoma of the twelfth dorsal vertebra which remained solitary for 5 years.

new bone extend from a myelomatous lesion creating an appearance similar to that of osteogenic sarcoma. A third pattern is that of generalized, fairly uniform sclerosis. It goes without saying that cases presenting such unusual bone pat-



FIG. 19. There is a large area of severe bone destruction crisscrossed by surviving trabeculae in the ilium. The appearance is that of a bizarre reticular pattern. This is a common pattern for myeloma in the ilium. A lesion of this type is often the initial manifestation of myelomatosis, occurring as a single plasmacytoma for varying periods of time. In this case the skeleton showed evidence of diffuse myelomatosis.

terns require very careful study to exclude conditions which are more commonly associated with osteosclerotic manifestations. It may be rewarding, on occasion, however, to keep in mind that such changes have been reported in multiple myeloma. Primary osteosclerosis in myelomatosis is, in addition, to be distinguished from secondary sclerosis which may occur following treatment by radiotherapy or urethane or as a result of amyloid deposition.



FIG. 20. Reticulated area of severe bone destruction involving the proximal tibia in a 48 year old man. The surrounding bone is normally mineralized. This lesion was the only skeletal manifestation of a generalized myelomatosis which was evidenced by the finding of myeloma cells in the sternal marrow and by a characteristic serum protein electrophoretic pattern.

#### *8. Solitary Myeloma*

It is not unusual to find a plasmacytoma in some portion of a skeleton not otherwise demonstrably affected by myelomatosis. In the vast majority of such cases, however, multiple areas of bone destruction due to generalized disease develop within a few months or, at the most, two or three years after the initial

observation. In addition, in most cases where only a single lesion is found, sternal marrow puncture will reveal evidence of generalized myelomatosis or biochemical and electrophoretic studies will reveal evidence of myeloma proteins. On rare occasions, however, single plasmacytomas may occur and remain solitary for many years without any roentgen or laboratory evidence of generalized disease. To this type of lesion the term "solitary myeloma" may be justifiably



FIG. 21. Myelomatous involvement of rib with soap-bubble pattern. The posterior portion of the fifth left rib is the site of a large destructive lesion which is compartmented by coarse septae. The affected bone is expanded and its cortex is thinned. There were no other skeletal lesions and sternal marrow smear, serum and urine protein electrophoresis revealed no evidence of myelomatosis. Biopsy of the rib lesion, however, showed unmistakable plasmacytoma (Courtesy of Dr. Richard Marshak).

applied. Experience has shown that in the presence of a single lesion the finding of myeloma proteins or the demonstration of myeloma cells in a sternal marrow smear usually presages the development of disseminated osseous involvement within a relatively short time.

Most of the single lesions, often erroneously referred to as solitary myeloma, occur in the pelvis, spine or ribs (Fig. 21). Many tend to show the trabeculated, soap bubble appearance. Others are represented by an area of severe bone destruction of homogeneous lucency (Fig. 17). Single myelomas are not uncommonly found as a cause for extradural compression of the spinal cord (Fig. 24).





## INTRAVENOUS UROGRAPHY AND MULTIPLE MYELOMA

Impairment of renal function is frequent in multiple myeloma. Various reports have indicated that kidney changes occur in from 48 to 90 per cent of myeloma patients and next to pneumonia, uremia is considered to be the most common cause of death in this disease. Abnormal myeloma protein passes the glomerular membrane and precipitates as laminated casts all through the tubular system. The resulting blockage of the renal tubules is one of the chief causes of renal insufficiency. Paramyloidosis and other forms of abnormal protein damage may also play some part in the impairment of renal function. Recently, Sanchez and Domz (18) have classified the renal syndromes which may be associated with multiple myeloma. These include: acute glomerulonephritis,



FIG. 23. Indeterminate type pattern in myelomatosis. There is a diffuse demineralization overlaid by focal, poorly defined radiolucencies.

adult Fanconi's syndrome, renal tubular acidosis, acute tubular necrosis and acute and chronic pyelonephritis. It is apparent, therefore, that myeloma may masquerade as primary kidney disease, especially in occult multiple myeloma where more tangible signs of the disease are absent.

Evidence is now accumulating which indicates that there is a distinct danger in performing intravenous urography on patients with multiple myeloma (19-22). In most of the reported cases the urographic examination has precipitated acute renal failure. At postmortem examination cast-plugged tubules are the outstanding finding. Perillie and Conn (22) have expressed the belief that precipitation of intratubular proteins is the main factor involved. Cathartics, enemas and withdrawal of fluids preparatory to the examination result in various

FIG. 22. Moderate myelomatous honeycombing of the shaft of the humerus. There is diffuse destruction crisscrossed by surviving trabeculae. Breast shadow overlies the lower half of the shaft. There are several circumscribed areas of lysis with dense peripheries in the head and neck of the humerus. A honeycomb pattern is seen also along the axillary border and at the glenoid and acromion process of the scapula. The outer end of the clavicle is similarly involved. Milder forms of this pattern without associated circumscribed lesions differ from normal bone architecture only in that the reticulation is more diffuse and exaggerated.

degrees of dehydration, and abdominal compression to block the flow of the contrast containing urine reduces renal blood flow and further increases the



FIG. 24. There is a destructive lesion involving the posterior portion of the body of the second lumbar vertebra with extension into the pedicles. The tumor compresses the spinal cord. Biopsy specimen was reported as myeloma. There was no other skeletal involvement but the sternal marrow smear revealed myeloma cells and serum protein electrophoresis showed changes characteristic of myelomatosis. These latter findings suggested there would probably be early disseminated skeletal changes.

urinary concentration. The precipitation of the abnormal proteins is thereby enhanced. As a result the tubules are plugged and there is an obstructive uropathy with subsequent oliguria, anuria and death (23).

Although most cases of renal insufficiency due to myeloma are characterized

by an absence of hypertension, some cases do present a dominant clinical picture of hypertensive azotemia. In such cases, the clinician may well request intravenous urography in the hope of uncovering a correctable renal lesion. Such a case has been reported by Sanchez and Domz (18).

Leucutia (23) has provided a brief but lucid review of this problem and recommends that intravenous urography should not be performed in frank cases of multiple myeloma for any reason. In cases of proteinuria of undetermined cause, the possibility of myeloma masquerading under the guise of a nephropathy should be considered and intravenous urography performed only after such a possibility has been eliminated by electrophoretic studies of the blood and urine proteins.

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## DESOXYRIBONUCLEASE I ACTIVITY IN THE DUODENAL JUICE AND SERUM OF MAN

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Although the desoxyribonucleic acid depolymerase with an acid pH optimum, desoxyribonuclease II (DNase II), is found in a wide variety of animal tissues (1), desoxyribonuclease I (DNase I) with a pH optimum of 6.8 to 8.2 is found in large amounts only in the pancreas (1, 2). Recently, DNase I activity has been found in lesser amounts in other tissues using techniques which are postulated to activate the enzyme and inactivate its inhibitors (3, 4).

Significant DNase I activity has been reported to be present in the pancreatic juice of the dog (1), the duodenal juice of man (5), and the serum of man and various animals (5-8). Although Kowlessar and McEvoy mention in passing that a reduced DNase I activity was found in the duodenal juice of patients with pancreatic fibrosis, they presented no quantitative data regarding activity in the duodenal juice of normal subjects, patients with pancreatic disease, or patients with other disease states (5). A review of the literature has failed to reveal any additional data concerning DNase I activity in human duodenal juice. Serum DNase I activity has been reported to be elevated in patients with acute pancreatitis (5) and in animals with certain forms of experimental pancreatitis (6), particularly when associated with significant tissue necrosis. The activity in the sera of patients with a variety of other disorders have been reported to be normal (5, 8) or depressed (7) and in malignancies it has been reported to be normal (8), elevated (9), or depressed (7).

The current study was undertaken to determine DNase I activity in the duodenal juice and in the serum of normal subjects and of patients with chronic pancreatitis, pancreatic carcinoma, and a variety of benign and malignant non-pancreatic diseases.

### MATERIALS AND METHODS

Duodenal juice was obtained by aspiration through a double lumen tube positioned fluoroscopically during the performance of a standard secretin test, as described from this laboratory by Dreiling (10). Sixty-two subjects were studied, including 19 normal controls, 8 with chronic pancreatitis, 11 with carcinoma of the pancreas, 5 with other intra-abdominal malignancies, 7 with peptic ulcer or inflammatory bowel disease, and 12 with miscellaneous non-neoplastic diseases. In all subjects, DNase I activity was determined in an aliquot of the pooled 80 minute collection of duodenal juice following the intravenous administration of

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Supported in part by a grant from the National Institutes of Health, United States Public Health Service, Grant No. 2A-5126.

one unit of secretin per kilogram of body weight. In 45 of these subjects, enzyme activity was determined in an aliquot of unstimulated duodenal juice obtained prior to secretin injection. In 15 of the subjects, the duodenal juice was analyzed following administration of 100 units of pancreozymin intravenously eighty minutes after the secretin. The serum of 58 of these subjects, collected before secretin injection, was also studied. In addition, serum alone was studied in an additional 68 patients including 48 with miscellaneous nonmalignant nonpancreatic disease, 15 with malignancies including carcinoma, lymphoma, and leukemia, and 5 with systemic lupus erythematosus.

DNase I activity was determined by a modification of the method of Donahue, Houek, and Coffey (6). Analyses were either performed immediately or the specimens were stored at  $-15$  to  $-20^{\circ}\text{C}$  after it had been shown that activity was not altered by such storage. All determinations were done in duplicate. Preliminary studies of duodenal juice and serum showed the pH optimum in various specimens to range between 7.0 and 7.5 so all determinations were performed at a pH of 7.3. 0.5 ml of a solution containing 600  $\mu\text{g}$  of DNA (Schwarz) dissolved in Veronal buffer (pH 7.3) and with a concentration of 0.04M magnesium chloride was incubated with an equal volume of duodenal juice or serum diluted 1 to 10 with the Veronal buffer for thirty minutes at  $37^{\circ}\text{C}$ . The enzyme activity was halted by the addition of 5.0 ml of 0.10M acetate buffer (pH 3.7) containing 0.4 mg per milliliter of serum albumin and 1 mg per milliliter of Knox gelatin. After the addition of this reagent, the mixture was allowed to stand for five minutes at  $37^{\circ}\text{C}$  during which time the acidified serum albumin formed a stable turbid colloid with the polymerized DNA remaining after enzyme action.

The absorbency of the turbidity so produced was determined at 450  $m\mu$  in a Coleman Junior Spectrophotometer. Since the color of the various specimens affected the optical density readings, duplicate control determinations were done on each specimen by incubating the diluted duodenal juice or serum with the acidified albumin reagent and subsequently adding the DNA substrate. The difference between the control and test readings was compared to the optical density produced by various amounts of polymerized DNA and translated into micrograms of DNA depolymerized. Concentration of enzyme activity in duodenal juice and serum was recorded as the amount of substrate depolymerized (Sd) expressed as micrograms of DNA depolymerized by 0.05 ml of duodenal juice or serum in thirty minutes at  $37^{\circ}\text{C}$ . Output of enzyme activity in duodenal juice after secretin was calculated by multiplying Sd by 20 to convert to per one ml of duodenal juice and multiplying this by the volume output in ml per kilogram of body weight in the eighty minutes following secretin administration.

## RESULTS

The experimental results are summarized in Tables I and II. Significant DNase I activity was found in the unstimulated and secretin-stimulated duodenal juice in the various subgroups. In all determinations, the concentration in the duodenal juice was always less than in the serum of the corresponding subject. In the unstimulated juice, the mean concentrations in the patients with

chronic pancreatitis and intra-abdominal malignancy were less than in the other groups but the ranges and variability in all groups were so great that the differences were not statistically significant. The mean concentrations in the secretin-stimulated duodenal juice were somewhat closer and the standard deviations were just as large so that differences were again not statistically significant. Similar results were found in the duodenal juice of the 15 subjects studied with pancreozymin. Output of enzyme in the duodenal juice after secretin was significantly lower in the pancreatic carcinoma patients than in the

TABLE 1  
*Duodenal Juice Desoxyribonuclease I Activity\* and Output\**

Diagnosis	Unstimulated			Secretin-Stimulated		
	No. of Subjects	Mean DNase I Activity†	No. of Subjects	Mean DNase I Activity†	Mean DNase I Output†	Mean Volume Output‡ of Duodenal Juice
A. Chronic pancreatitis	7	24 ± 32 (2-85)	8	44 ± 26 (10-90)	2800 ± 2200 (600-5900)	3.0
B. Pancreatic carcinoma	7	44 ± 31 (2-95)	11	44 ± 21 (12-73)	1600 ± 1800 (300-5300)	1.6
C. Other intra-abdominal malignancies	4	28 ± 36 (5-82)	5	43 ± 39 (5-95)	4000 ± 3900 (300-8400)	4.1
D. Peptic ulcer and inflammatory bowel disease	5	49 ± 16 (25-60)	7	60 ± 36 (8-125)	6900 ± 3800 (2400-13300)	5.3
E. Miscellaneous diseases	10	39 ± 30 (5-100)	12	47 ± 34 (5-105)	4100 ± 3700 (400-11600)	4.3
F. No disease	12	56 ± 34 (5-95)	19	53 ± 31 (5-113)	4700 ± 3600 (600-13100)	4.4

\* Units of activity and output and method of calculation described in text

† Values represent mean ± standard deviation

Values in parenthesis represent range

‡ Volume of duodenal juice expressed as ml per kilogram of body weight in the 80 minutes following secretin

normals ( $P$  between 0.02 and 0.01). Output in the chronic pancreatitis patients was lower; in the ulcer and intestinal inflammatory disease patients, the enzyme output was higher than in the normals, but the differences were not significant.

Serum DNase I activity was equally low in the patients with pancreatic carcinoma and in those with other malignancies and the mean serum activity in the thirty patients with malignancy was significantly lower ( $P < 0.01$ ) than in the normal controls and in those with non-neoplastic diseases. However, there was a great deal of overlap since 6 of the 18 controls and 26 of the 65 patients with miscellaneous diseases had serum values of 115 or less and 10 of the thirty patients with malignancy had values of 115 or greater. The mean of the miscellaneous group was less than the control group but the difference was not statis-



tically significant. The mean serum values in the patients with chronic pancreatitis and in those with lupus erythematosus were only slightly greater than in the controls.

#### DISCUSSION

The conditions used for enzyme activity assay were slightly different than reported for serum by Houck (11), but the mean value in normals of 134 using 0.05 ml of serum is similar to the value of 130 in 0.04 ml of serum found by

TABLE II  
*Serum Desoxyribonuclease I Activity\**

Diagnosis	No. of Subjects	Mean Activity	Range	Standard Deviation
<i>Subjects with simultaneous duodenal juice studies</i>				
A. Chronic pancreatitis	8	137	110-177	24
B. Pancreatic carcinoma	10	99	65-125	24
C. Other intra-abdominal malignancies	5	103	78-120	31
D. Peptic ulcer and inflammatory bowel disease	6	119	75-170	32
E. Miscellaneous diseases	11	134	73-180	32
F. No disease	18	132	68-165	31
<i>Subjects with serum alone studied</i>				
G. Nonpancreatic malignancies	15	99	53-130	20
H. Miscellaneous diseases	48	118	45-217	31
I. Systemic lupus erythematosus	5	137	80-185	33
<i>Summary</i>				
1. No disease (Group F)	18	132	68-165	31
2. Miscellaneous disease (Groups D, E and H)	65	121	45-217	32
3. Malignant diseases (Groups B, C and G)	30	100	53-130	20

\* Activity recorded as amount of substrate depolymerized (Sd) expressed as micrograms of DNA depolymerized by 0.05 ml of serum in 30 minutes at 37°C.

Houck. For duodenal juice, we used the same conditions as for serum. Houck has reported that the optimum conditions for crystalline pancreatic DNase activity differ from the serum DNase, the former requiring a pH of 5.9 and a temperature of 20°C (11). However, other workers, using other techniques, have found higher pH optima for pancreatic DNase (pH 6.8 to 8.2) (1, 2) and we found the pH optimum for duodenal juice to be approximately 7.3. In addition, Houck found significant DNase activity at higher than the optimal pH and temperature. Consequently, even if the conditions for duodenal juice activity were not fully optimal, since all duodenal juice specimens were measured under the same conditions, a constant fraction of maximal activity should have been obtained, which would still be valid for comparative purposes. It should be

stressed, however, that activities rather than actual amounts of the enzyme present were measured, so that variations in the amounts of activators and inhibitors present, as well as in the amount of enzyme present would contribute to the final values obtained (12, 13).

Although the numbers in each group are relatively small, the variability and overlap for duodenal juice are such that even if a larger series were to show significant differences between the mean concentrations, it is unlikely that such differences would be clinically valuable. Since the mean concentration in the secretin-stimulated duodenal juice of the pancreatic carcinoma patients was only slightly below that of the controls, the significantly lower output is predominantly a function of the significantly lower volume output characteristic of such patients. The serum activity in the patients with malignancies was significantly lower than the other groups, in accordance with the findings of Wroblewski and Bodansky (7) but opposed to the reports of Kurnick (8) and Chepinoga (9). Again the variability and overlap are such that the difference is probably not clinically valuable. The patients with chronic pancreatitis had serum values only slightly above normal as opposed to the markedly elevated values reported in acute hemorrhagic pancreatitis. The patients with systemic lupus erythematosus had only slightly higher than normal values, as previously reported by Kurnick *et al.* (14).

#### SUMMARY

1. Significant desoxyribonuclease I (DNase I) activity was found in the unstimulated and secretin-stimulated duodenal juice and in the serum of normal controls and of patients with chronic pancreatitis, pancreatic carcinoma, and a variety of malignant and nonmalignant diseases.

2. Although some minor differences were found in the duodenal juice activity of the various groups, the differences were not significant. Enzyme output after secretin was significantly less in the pancreatic carcinoma group, as a function of the significantly lower volume, since the concentration was only slightly below the controls. In all groups, duodenal juice activity was always less than serum activity.

3. In the patients with malignancies (both pancreatic and nonpancreatic) the mean serum activity was significantly less than in the normals and in the patients with other diseases, but the variability and overlap were such that the difference is probably not clinically valuable.

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# MESENTERIC HERNIAS IN INFANCY AND CHILDHOOD

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Mesenteric hernias are considered to be unusual in any age group, but Gross stated that they are the most common of intra-abdominal hernias in the childhood period (1). A review of the literature revealed 34 cases of mesenteric hernia in infancy and childhood (2-21). The largest number of cases observed was at the Children's Hospital, Boston, reported by Cutler, where operations were performed on four infants and children with mesenteric hernia (3). The remaining authors reported single cases.

A diagnosis of mesenteric hernia has not been recorded prior to operation. The purpose of this paper is to report a case of mesenteric hernia, and to present a review of the reported cases.

## CASE REPORT

### *History*

S.W., a white female, was admitted to The Mount Sinai Hospital, New York, on May 15, 1956, at 48 hours of age. There were no siblings. The pregnancy was normal and full-term. The birth weight was 3.3 kg. At the age of 39 hours the infant began to have persistent vomiting of bile-stained fluid. No meconium had been passed. At that time, examination revealed abdominal distension and hemorrhagic discoloration of the skin of the abdominal wall. A plain film of the abdomen showed a dilated loop of intestine on the right side and a density suggesting fluid. A repeat film, seven hours later, revealed additional dilated loops of intestine, and free air under the right diaphragm (Fig. 1A and 1B).

### *Clinical Findings*

The infant was well nourished and weighed 3.1 kg. The cry was weak. The abdomen was distended and no masses were palpable. Bowel sounds were not heard. There was hemorrhagic discoloration of the skin in both flanks. On rectal examination, a mass was palpable in the pelvis. Slight icterus was noted.

### *Laboratory Findings*

Hemoglobin was 17 Gm/100 ml; leukocytes 14,300 with a differential count of 75 segmented and 5 band form neutrophils and 20 lymphocytes. Urinalysis showed a few leukocytes.

The clinical diagnosis was meconium peritonitis due to perforation of the small intestine secondary to intestinal obstruction.

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### *Operation*

A cut-down intravenous was started in an ankle vein, and operation was performed two hours after admission. Under ether anesthesia, a transverse incision above the umbilicus was made. On opening the peritoneal cavity hemorrhagic fluid, meconium and air escaped. A mass of small intestine, dark blue in color, adherent to the pelvic wall near the bladder was seen in the lower abdomen. When these loops were freed and mobilized, a large defect in the mesentery of the terminal ileum and ascending colon, measuring about 4 cm in length could be seen. Loops of terminal ileum had passed through this defect and twisting

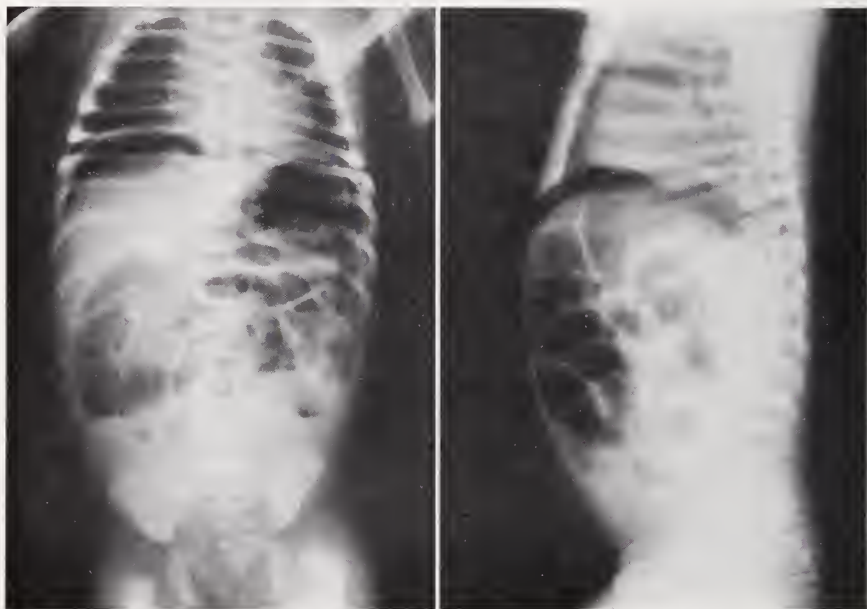


FIG. 1. A, RGs of abdomen preoperatively, showing a density in the lower abdomen suggesting fluid, dilated loops of intestine, and free air under the right diaphragm. B, lateral view showing the above findings.

upon themselves, had formed a volvulus. The resultant ischemia produced an area of hemorrhagic infarction, measuring about 10 cm in length as well as a large perforation in the antimesenteric surface of the loop which had been adherent to the pelvic wall. About 30 cm of grossly strangulated ileum was excised. The distal line of resection was about 1 cm proximal to the ileocecal valve. An end-to-end anastomosis of the cut ends of the ileum was performed. Large amounts of meconium were washed from the peritoneal cavity with saline solution. Some loops of small intestine were heavily coated with meconium. The colon was small in size and empty. The abdomen was closed without drainage. Sixty ml of blood were given during operation.

### *Report of Pathology*

The pathologic report was "segment of small intestine, measuring 32 cm in length, showing acute hemorrhagic infarction of twisted loop with perforation

and acute meconium peritonitis; localized area of gangrene with impending perforation at site of constriction from hernial ring; proximal and distal lines of resection were outside the infarcted segment" (Fig. 2).

#### *Course*

The temperature remained normal throughout the postoperative course. The parenteral fluids were continued for three days. Gastric syphonage and oxygen were administered for two days. Oral feedings were started on the third day. One Gm of chloramphenicol and 2 million units of penicillin were given daily for one week. Meconium stools were passed on the first day, followed by greenish, and then normal stools by the eighth day. The wound healed by primary



FIG. 2. Operative specimen segment of ileum involved in mesenteric hernia.

union. The infant was discharged on the twelfth day. She has remained well for a period of five years (Fig. 3).

#### DISCUSSION

Mesenteric hernias are intraperitoneal hernias which have no sac but consist in the protrusion of a loop of bowel through a defect in the mesentery. In the collected 35 cases, such herniation has been complicated by intestinal obstruction, frequently strangulation and necrosis of varying lengths of intestine. The terminal ileum is the segment of bowel most commonly herniated through the defect.

The defect was in the mesentery of the terminal ileum in thirty cases; in two instances in the mesentery of the midileum, and in two in the jejunal mesentery. In one infant there were multiple openings along the terminal 20 cm of the ileal mesentery, through one of which, bowel had passed and became obstructed.

In the majority of instances the openings were quite small, averaging 2 to 3 cm in diameter. They were usually oval or round in shape with smooth, peritonealized edges.

The etiology of mesenteric defects is usually explained by the theory of coalescence of the mesothelium in an avascular area during embryonic life. According to Treves, there is an avascular area in the mesentery of the ileocecal region circumscribed by the anastomosis between the ileocolic artery and the last intestinal artery supplying the terminal ileum (22). The mesentery of this region is poorly supported and contains neither fat, lymph nodes, nor visible blood vessels. There has been an occasional history of abdominal trauma shortly preceding the clinical manifestations of intestinal obstruction, but in only one child were the edges of the defect roughened.



FIG. 3. Patient at four years of age.

The size of the defect does not limit the length of prolapsed bowel. It is probable that with the accidental protrusion of a knuckle of bowel through the ring-like opening, distention results in a "gas trap" mechanism, and this is the force that draws loops of bowel through the aperture until incarceration occurs.

In 18 cases (51% of this series) gangrenous bowel was found. The duration of symptoms in these instances varied from eight hours to four days. Volvulus of the afferent and efferent loops of the incarcerated intestine was a serious complication producing early necrosis. This occurred in seven cases.

Additional intestinal anomalies were seen in the reported cases. In two infants, five days and three weeks of age, there was volvulus of the midgut, and, in an infant 32 hours old, there was atresia of the ileum.

The ages of patients in the 35 recorded cases of mesenteric hernia in infants

and children varied from 2½ hours to 19 years, as follows:

No. of Cases	Ages
13 (37%)	0 to 1
2	1 to 5
8	5 to 10
7	10 to 15
5	15 to 20

Both sexes were represented: 23 males (66%) and 12 females (34%).

The symptoms of mesenteric hernia were those of acute intestinal obstruction—abdominal pain, vomiting, and obstipation. Bile-stained vomitus was an early symptom in the newborn infant. A shock-like state was often associated with necrosis of the incarcerated intestine.

On examination, the infants appeared listless and the children acutely ill. Varying degrees of abdominal distention were noted. Either the high-pitched sounds of increased intestinal peristalsis, or absence of intestinal activity in cases with necrosis of the bowel were found on physical examination. Tenderness and spasm of the abdominal musculature were usually present, but were not as obvious in the newborn infant. A mass produced by volvulus of the intestine was occasionally palpable. As the obstruction continued, the usual changes secondary to dehydration were noted: poor skin turgor, decreased urinary output, and fever.

The laboratory findings were essentially those of acute intestinal obstruction. Plain roentgenograms of the abdomen in the recumbent and upright positions showed small intestinal obstruction. Free air under the diaphragm was seen in cases with perforation of a gangrenous loop of intestine.

Treatment of mesenteric hernia has consisted of reduction or resection, depending upon the condition of the intestine, followed by closure of the defect in the mesentery. The procedure and results were as follows:

Procedures	No. of Cases	Number Dead	Number Living	Per Cent Survival
Reduction	14	1	13	93
Resection and primary anastomosis	10	3	7	70
Staged Mikulicz resection	2	0	2	100
Resection and ileostomy	1	1	0	0
Laparotomy alone	3	3	0	0
No operation (postmortem finding)	5	5	0	0
Total	35	13	22	63

The results of operations for mesenteric hernias in infants under one month of age were encouraging. Four of the 11 infants under one month of age had meconium peritonitis and necrosis of the ileum. Among these there was one case with recovery after intestinal resection and primary anastomosis; one case with recovery after several staged exteriorization procedures; one death after intestinal resection and ileostomy, and one death after laparotomy only. Of the seven infants without meconium peritonitis, there were five recoveries after intestinal reduction, and one recovery after intestinal resection and primary



anastomosis. The remaining infant had no operation and died. In summary, there were 11 infants under one month of age (four with meconium peritonitis) with eight recoveries, a survival rate of 73 per cent. The survival rate was 63 per cent for all age groups combined.

#### SUMMARY

The pathologic and clinical features and the treatment of mesenteric hernia in infancy and childhood of 34 cases in the literature, have been analyzed and discussed. An additional case of mesenteric hernia is presented.

Mesenteric hernia was usually noted in male infants under the age of one year and in male children from 5 to 15 years of age. The presenting complaint was acute intestinal obstruction.

The survival rate was 63 per cent for all age groups combined, and 73 per cent for infants under the age of one month.

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# CRYPTOCOCCAL MENINGO-ENCEPHALITIS ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Cryptococcosis (torulosis, European blastomycosis) is a world-wide fungal disease caused by the organism *Cryptococcus neoformans* (*C. hominis*, *T. histolytica*). There are well over 300 cases on record; comprehensive reviews of large series include that of Cox and Tollhurst (1), Evans and Harrell (2), and Littman and Zimmerman (3). The primary portal of entry of the organism is believed to be the respiratory tract with air-borne transmission by infected dust particles from soil. Pigeon excreta have been found heavily contaminated with virulent strains of *C. neoformans* and may serve as a focus of infection (3-5). The vast majority of reports are of cases of leptomeningitis and meningo-encephalitis with an indolent course resembling that of either tuberculous meningitis or an expanding intracranial lesion. A significant number of cases occur in association with diseases of the reticuloendothelial system, particularly in Hodgkin's disease, but also leukemia, lymphosarcoma, giant follicular lymphoblastoma, Boeck's sarcoidosis, and multiple myeloma (1, 3, 6, 7).

It is our purpose to describe a case of central nervous system cryptococcosis in which for the first time to our knowledge there subsequently developed a clinical picture of systemic lupus erythematosus (SLE) with a positive L.E. preparation, and to investigate the possibility of a relationship between cryptococcosis and SLE.

## CASE REPORT

A 50 year old white female first noted headaches and an unsteady gait in November, 1956. In addition, her family observed her to be less spontaneous in her motivation, and progressively withdrawn. Two weeks prior to the onset of her symptoms her mother died, and her family felt that her depression and complaints could be causally related. Her local physician referred her to a neuropsychiatrist who suggested shock therapy for depression. By mid-December, 1956, she became nauseated and manifested a tendency to fall to the right side on walking. In addition, she complained of tinnitus and some hearing loss on the right side. A few days later, drooping of the right side of the face developed.

The past history was essentially noncontributory. She had lived most of the time in the New York area, save for a period in Cleveland, Ohio, in the nineteen forties. Appendectomy was performed at the age of 10; at age 18, because of hyperthyroidism with exophthalmos, she received radiotherapy to the thy-

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roid with remission. She had two sons in good health. Menses had recently become irregular. The remainder of the systemic review was within normal limits.

Physical examination on December 24, 1956 disclosed a well-developed middle-aged woman with diminished psychomotor activity who was rational and whose speech was intact. There was a right peripheral VIIth nerve paresis (Bell's palsy) and a moderate exophthalmos (old). She was ataxic with a tendency to fall to the right. The right pupil measured 4 mm; the left 6 mm; both reactive. The fundi were normal. The visual fields were normal. There was tenderness over the right mastoid bone. Air conduction was diminished on the right. Corneal reflexes were intact, as were the remaining cranial nerves. Deep tendon reflexes were equal and active and there were no pathologic reflexes. Strength was equal in all extremities. Sensory examination was normal. On Romberg testing the patient swayed markedly to the right and there was terminal dyssynergia on finger to nose testing, more on the right. Blood pressure was 130/80. The general physical examination otherwise showed no abnormalities.

Routine laboratory studies showed hemoglobin 14.7 Gm%; hematocrit 41%; WBC count 13,400/mm<sup>3</sup>; differential count yielded segmented forms 71%, non-segmented 10%, lymphocytes 13%, and monocytes 6%; erythrocyte sedimentation rate was 72 mm/hr. (Westergren); serology was negative; urinalysis normal; stool was negative for occult blood. Chest x-ray showed the heart, lungs, and bony thorax to be within normal limits.

The impression was that of a space-occupying lesion at the right cerebello-pontine angle with involvement of the VIIth and VIIIth cranial nerves. In view of the rapid sedimentation rate, the possibility of metastatic disease or a brain abscess was considered. Accordingly, on December 27, 1956, a spinal tap was done at L 4-L 5 revealing an opening pressure of 150 mm water with free rise and fall. The fluid was clear and colorless with 26 cells/mm<sup>3</sup>, mostly mononuclears; protein 210 mg%; sugar 53 mg%; chlorides 710 mg%; routine bacterial culture negative. Skull x-rays were normal, including the petrous pyramids and internal auditory meati. The pineal was not calcified. An electroencephalogram was nonlocalizing.

On January 2, 1957 the patient was admitted to Meadowbrook Hospital for further studies to rule out metastatic disease, and for probable neurosurgical intervention. A repeat spinal tap showed an opening pressure of 210 mm water with normal dynamics and clear, colorless fluid with 17 mononuclear cells/mm<sup>3</sup>; protein 350 mg%; chlorides 713 mg%; sugar 42 mg%. Blood chemistries included BUN 10 mg%; fasting blood sugar 106 mg%; HCO<sub>3</sub> 27 mEq/L.; chlorides 102 mEq/L.; calcium 11.4 mg%; phosphorus 3.4 mg%; alkaline phosphatase 10 King-Armstrong units (KAU); total protein 6.7 Gm% with albumin 4.7 Gm% and globulin 2.0 Gm. Sternal bone marrow was within normal limits. Chest x-ray, gastrointestinal series, barium enema and intravenous pyelogram were all within normal limits. Audiometric studies showed a mixed conduction and perception deafness on the right, and there was no response to caloric testing of the right ear. In view of the absence of evidence of metastatic disease, neurosurgical intervention was deemed indicated. On January 14, 1957, a ventriculogram and pneumoencephalogram were performed and the ventricular



system was found normal. Because of the localization of a lesion of the VIIth and VIIIth nerves and cerebellar pathways on clinical evidence, it was felt that the cerebello-pontine angle should be explored. At surgery, the cerebellar hemispheres appeared normal with no distortion and under no increased tension. On lifting the cerebellum from its bed, the petrous pyramid and internal auditory meatus were found to be normal, and both the VIIth and VIIIth nerves clearly demonstrated. A cerebellar biopsy revealed normal cerebellar tissue. The postoperative period was uneventful, and during her entire hospital



FIG. 1. April 1957—note the scattered papulo-erythematous lesions on the face and forehead and the ulceronecrotic lesions of the lips.

stay, the patient remained afebrile. She was discharged to a convalescent home January 31, 1957, essentially unchanged from admission.

In April, 1957 she was seen again, complaining of fever and soreness of the mouth of two weeks duration. She appeared emaciated and slightly obtunded, and the temperature was 102°F. There were scattered, pea-sized papular lesions on the forehead, face and upper chest, with surrounding erythema. In addition, there were ulceronecrotic lesions of the lips with cracking and bleeding (Fig. 1). Numerous shallow ulcerations were seen on the buccal mucosa, and there were serpiginous ulcers on an erythematous base on the hard and soft palate. The finger tips, thenar eminences, and soles of the feet revealed tender, sharply-defined erythematous, dime-sized macules. Tenderness could be elicited

in the small joints of the hands. There was no lymphadenopathy. The lungs were clear. Cardiac findings were normal, save for tachycardia of 120/min. The liver and spleen were not palpable. Neurological findings were unchanged. Hemoglobin was 12.5 Gm%; wbc count 4850  $\text{mm}^3$  and sedimentation rate (Westergren) 70 mm/hr. Because of the fever, skin and mucous membrane lesions, arthralgias and leukopenia, together with a protracted unexplained cerebral syndrome, the possibility of systemic lupus erythematosus came to mind. An L.E. clot preparation was strongly positive, revealing numerous rosettes, L. E. cells and free "globs" (Fig. 2).

After a four day trial on tetracycline, during which time the patient continued to be febrile at 101–102°F, she was admitted to the South Nassau Communities Hospital, Oceanside, N. Y. on April 23, 1957 for steroid therapy, with

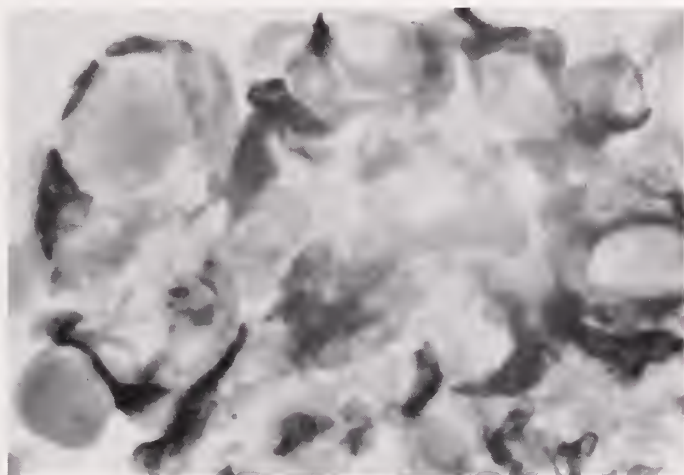


FIG. 2. A rosette of leukocytes showing L.E. cells.

a diagnosis of systemic lupus and cerebral vasculitis. Initial laboratory findings were hemoglobin 11.3 Gm%; wbc count 5,050/cu mm; differential count: segmented cells 87%; lymphocytes 11%; monocytes 1%; eosinophiles 1%. Urinalysis normal; L.E. preparation positive; Coombs Test negative; bux 17 mg%; fasting sugar 100 mg%; total serum protein 6.3 Gm% with albumin 3.5 Gm and globulin 2.8 Gm%; ceph.-chol. flocculation 2+ in 48 hours; alkaline phosphatase 8.7 KAU. Serum paper electrophoresis showed a normal protein distribution with no abnormality in gamma globulin. A spinal fluid before the administration of steroids was clear and colorless with pressure of 140 mm water; 3 cells per cu mm; protein 83 mg%; sugar 34 mg%; and chlorides 700 mg%. During the first four hospital days, she remained febrile and became somewhat confused. On April 26, 1957, prednisone was started, 20 mg every six hours. There was a precipitous drop in temperature within six hours to 96°F, and the patient remained afebrile thereafter, while the dosage of prednisone was progressively reduced. There was steady improvement of skin and mucous membrane lesions, loss of

joint tenderness and improved hydration. However, she continued to display progressive lethargy. On April 30, 1957, another spinal tap was done with pressure of 110 mm water and clear fluid. Again 3 cells/cu mm were seen and protein was 62 mg%, sugar 61 mg%. By May 2, 1957, there was spastic paresis of the left upper extremity with a positive Hoffman reflex. On the next day the patient was semicomatose. She was then transferred to Meadowbrook Hospital. Nuchal rigidity developed on May 7, 1957, and another spinal tap was done. It yielded clear, colorless spinal fluid, under a pressure of 510 mm of water. No cells were seen; protein 105 mg%; chlorides 655 mg%; sugar 74 mg%. Three L.E. preparations from peripheral blood were positive. Incubated sternal marrow also revealed L.E. cells. The patient became opisthotonic, was placed on ACTH, and also given intramuscular injections of high white count blood (8). She became comatose and expired on May 15, 1957, six months after the clinical onset of her illness. Final clinical diagnoses were systemic lupus erythematosus and cerebral vascular disease secondary to lupus. Cryptococcal meningitis was not suspected.

#### POSTMORTEM FINDINGS

The deceased was a well-developed, moderately well-nourished white female, 5'4" in length, weighing 130 pounds, who appeared much older than the stated age of 51 years. Small ecchymoses were noted over the lips and gums. Serous cavities were smooth, glistening and free of excessive fluid.

The thyroid, pancreas, adrenals, ovaries, pituitary, breasts, bone marrow, gastrointestinal tract and skin were grossly and microscopically within normal limits. The liver revealed fatty infiltration; a single leiomyoma was noted in the uterus; the aorta revealed mild atherosclerosis. The most significant gross finding was a severe bronchopneumonia of the right middle and both lower lobes. Microscopic examination also revealed pulmonary edema and mild chronic passive congestion.

The heart appeared to be normal upon gross examination. Microscopically, however, rare foci of endocardial inflammation were noted. These consisted of small areas of fibrinoid necrosis surrounded by small numbers of lymphocytes (Fig. 3). The kidneys likewise appeared normal grossly. Careful inspection of numerous sections, however, revealed rare glomeruli which exhibited a type of capillary glomerulosclerosis indistinguishable from the so-called wire-loop glomerulus of lupus erythematosus (Fig. 4). In addition, occasional arterioles contained smudgy hyaline thrombi. The spleen showed toxic splenitis, chronic passive congestion and focal chronic perisplenitis. Examination of numerous sections revealed occasional foci of concentrically-laminated periarterial sclerosis.

The surface of the brain was slightly dull. Sulci and gyri showed a normal configuration. Multiple cut sections of the brain (after formalin fixation) revealed a normal ventricular system. The pia-arachnoid appeared slightly thickened and opaque, especially within cerebral sulci. The intracranial vasculature was natural. Examination of cut sections of brain tissue with a hand lens revealed multiple minute cyst-like spaces (up to 0.1 cm) diffusely scattered in the super-

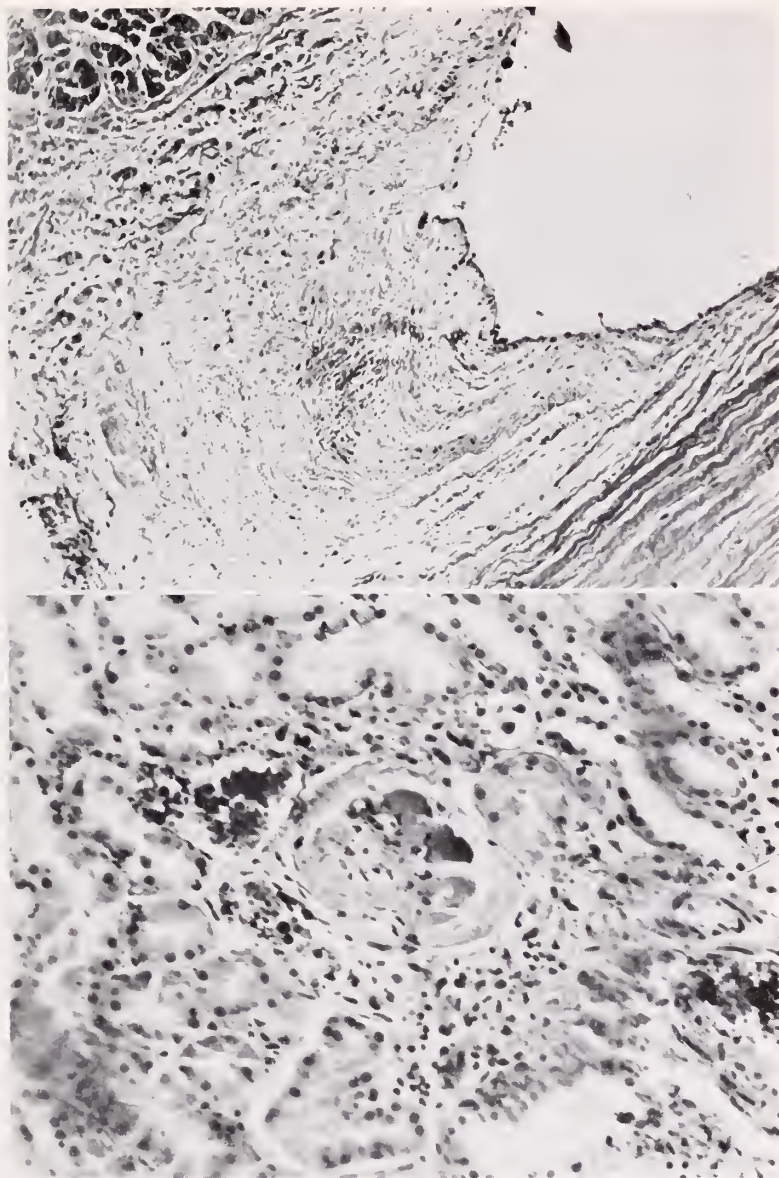


FIG. 3. Endocardium showing an area of fibrinoid necrosis with surrounding lymphocytic infiltration.

FIG. 4. Renal glomerulus showing focal hyaline fibrinoid necrosis of a capillary tuft.

ficial portions of the cerebral cortex. Microscopic examination of the brain revealed fibrous thickening of the meninges, infiltration by lymphocytes, plasma cells, and histiocytes, as well as accumulations of rounded periodic acid Schiff- and mucicarmine-positive organisms compatible with *Cryptococcus neoformans*. Accumulations of these organisms were also noted within cyst-like spaces in



the cerebral parenchyma, as well as in scattered colonies on the ventricular surfaces (Fig. 5, 6). Further study of other organs with mucicarmine and PAS failed to reveal additional foci of *Cryptococcus neoformans*.



FIG. 5. Cerebral cortex containing minute cyst-like spaces filled with *C. neoformans* and organisms infiltrating the meninges.

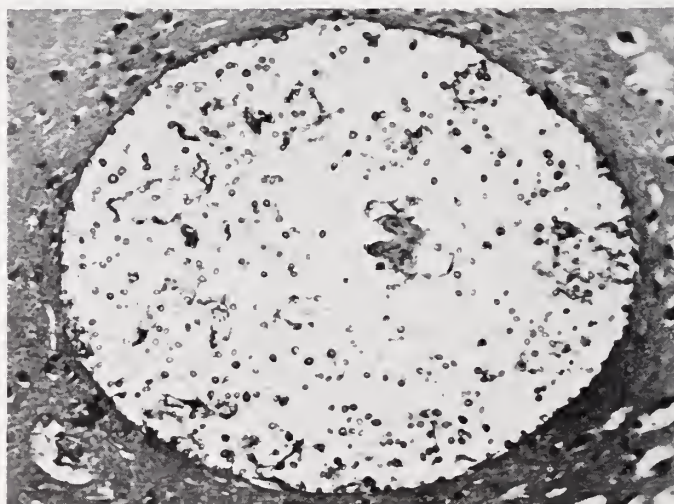


FIG. 6. High-power of one of the cyst-like spaces in cerebral cortex revealing *C. neoformans*.

It was felt that the characteristic lesions in the heart and kidney as well as the "onion-skin" sclerosis of the splenic arteries substantiated the clinical diagnosis of SLE. It should be noted that these lesions were found only after careful study of numerous sections.\*

\* We are indebted to Dr. H. Edward MacMahon, Professor of Pathology, Tufts University School of Medicine, for corroboration of these findings.

The final pathologic diagnoses were: chronic meningoencephalitis due to *Cryptococcus neoformans*; bronchopneumonia; and vasculitis consistent with SLE.

#### COMMENT

The diagnosis of cryptococcosis was made at postmortem on the basis of microscopic demonstration of cryptococcal organisms in large numbers in meninges and in minute cortical lesions. Confirmation of cryptococci was achieved by means of mucicarmine stain (3). Although cultures were not obtained, the morphological and staining characteristics of the organism and the characteristic tissue response were compatible with a diagnosis of cryptococcosis (Fig. 6).

The important question arose as to whether we were dealing with two co-existent, albeit unrelated diseases, cryptococcosis and SLE, or whether cryptococcosis had induced the syndrome of SLE.

Subsequent review of the medical literature revealed clinical protocols of other patients with cryptococcosis where features of the clinical syndrome were suggestive of SLE:

*Example 1.* Atkinson, Delaney and Miller described a 42 year old woman with "congenital hemolytic anemia" who developed fever, muscle and joint pains and headache and died of cryptococcal meningitis (9).

*Example 2.* (From case reports of the Mayo Clinic series: (10)) A 16 year old girl complained of progressive headache, anorexia, cough, low grade fever, and arthralgias. Examination disclosed a malar flush, ulcerated areas in the pharynx, early papilledema, and generalized lymphadenopathy. Laboratory studies included an elevated sedimentation rate, leukopenia of 1500 cells per cu mm, red cells and formed elements in the urine, and isoelectric T waves in all three standard leads of the electrocardiogram, suggestive of pericarditis. The patient died within six weeks. Although the protocol resembles that of SLE, postmortem examination revealed disseminated cryptococcosis. No mention is made of an L.E. preparation.

*Example 3.* One of us (S.P.) recently attended a 55 year old woman with inactive rheumatic heart disease who, two years previously, developed mild hemolytic anemia with low grade hyperbilirubinemia, palpable spleen, and elevated sedimentation rate. Three months later, she was hospitalized because of spiking fever to above 104°F associated with bilateral interstitial pneumonia. Numerous blood cultures remained sterile and antibiotics failed to alter the fever or clinical picture. Within hours of initiation of steroid therapy, however, there was dramatic clinical improvement. Steroids were discontinued in a few days. During the next nine months, the patient continued to display nightly temperature elevations ranging from 100.5° to 102°F and continued to have a moderate anemia and splenomegaly. Cardiac rhythmic disturbances complicated the clinical management. Chest x-rays showed a persistent left lower lung field infiltrate; on numerous occasions, L.E. preparations were examined because of the suspicion of SLE. These preparations were negative, as were antinuclear and anti-DNA complement fixation tests (kindly performed by Dr. Halsted Holman, see below). Finally, because of the development of mental confusion, drowsiness, occasional

vomiting, and an unsteady gait, cryptococcal meningitis was suspected and confirmed by recovery of the organism from the spinal fluid. A course of amphotericin B (11) was given intravenously with excellent results. The patient is now mentally clear with normal spinal fluid, although anemia and the pulmonary infiltration persist. In summary, this patient had clinical findings strongly suggestive of SLE despite the failure to show LE cells, after which cryptococcal meningitis appeared.

It is well recognized that cryptococcosis may appear at a late manifestation in patients whose host resistance has been altered by other primary debilitating diseases, especially those involving the reticuloendothelial system and especially in patients treated with steroids. Also, patients with long-standing SLE treated with steroids have succumbed to terminal cryptococcal meningitis (12, 13). In our case, however, the precedent illness was cryptococcal meningitis, SLE occurring terminally.

On the basis of these suggestive cases, the question was raised in our minds whether *C. neoformans*, or its products, could be etiologically responsible in this case for the syndrome of SLE and for the positive L.E. phenomenon. A possible explanation of the patient's systemic toxicity could be release of antigenically active components of the cryptococcal cell. For instance, capsular polysaccharides have been shown to react serologically with specific hyperimmune rabbit serum and have been differentiated into three types, A, B and C (14, 15). Analysis of the hydrolyzed polysaccharides by chromatography has led to the identification of the hydrolyzed products as the monosaccharides: xylose, mannose, galactose and glucuronic acid (16, 17). Serologically-reactive material in spinal fluid, blood and urine has also been demonstrated from a human case of cryptococcal meningitis by Neill, Sugg and McCauley (18). However, there was no evidence of disseminated disease in their patient and the blood and urine were free of cryptococci. Likewise, the spinal fluid was free of organisms at the time of study. Nevertheless, in their studies, rabbit antiserum gave high titer precipitin and complement fixation reactions with these fluids and prior absorption with exogenous capsular polysaccharide rendered this immune rabbit serum inert. Their case illustrates the passage of soluble cryptococcal products from brain and spinal fluid to the systemic circulation.

In an attempt to establish a relationship between cryptococcosis and SLE in our patient, the following studies were undertaken.

#### EXPERIMENTAL OBSERVATIONS

##### *Materials and Methods*

Serum from our case had been frozen at  $-20^{\circ}\text{C}$  for several months before studies were undertaken. Similarly preserved sera from three other cases of cryptococcosis were also studied. "Active" L.E. serum and normal plasma and serum were used. White cell "buttons" were prepared by means of buffy coat separation and centrifugation from sera of non-lupus subjects with rapid sedimentation rates. Other materials included cultures of *C. neoformans* and crypto-



coccal capsular polysaccharides A, B and C.\* L.E. cell formation was dependent upon: (1) presence of a serum lupus factor in the patient's serum; (2) a source of cell nuclei to be acted upon by the factor; and (3) viable white blood cells to phagocytize the affected nuclei (19). L.E. preparations were performed by mixing 0.5 to 1.0 ml of test serum or plasma with a white cell button and incubating at 37°C for one hour. Centrifuged cells were smeared, alcohol-fixed, and stained with Wright stain. L.E. criteria included the finding of L.E. cells, rosettes, and L.E. bodies ("globs"). Serologic studies were kindly performed by Dr. Halsted R. Holman at the Rockefeller Institute. Complement fixation and precipitin reactions using test sera were set up against nuclear antigens (whole nuclei, nucleohistone, or DNA) (20, 21). Similar immunologic studies were performed with cryptococcal polysaccharides A, B and C versus active L.E. serum.

### Results

1. The patient's serum consistently induced a positive L.E. phenomenon with donor white cells.

2. The patient's serum also gave a strong complement fixation reaction with nucleoprotein to a titer of 1:64. There was a negligible reaction of the patient's serum with DNA or whole nuclei.

3. Sera from three other cases of cryptococcal meningitis, however, failed to induce L.E. cells or to react with nuclear antigens.

4. Preparations of normal human serum or the serum of a patient with cryptococcosis to which had been added white blood cells (lupus preparation) plus living homologous *C. neoformans* resulted merely in phagocytosis of the organisms. No L.E. criteria were found.

5. Leukocyte L.E. criteria were also sought for by adding white cell buttons to normal plasma or cryptococcal serum which had undergone prior incubation for 36 hours with living cryptococci (22). No L.E. criteria were found, however.

6. Incubation of cryptococcal polysaccharides A, B and C with leukocytes resulted in intact cells without L.E. criteria.

7. Cryptococcal polysaccharides added to L.E. serum gave a negative complement fixation reaction in the test tube and a negative precipitin reaction on an agar plate employing the Ouchterlony technique.

8. Addition of cryptococcal polysaccharides to L.E. serum or to the serum of our patient neither enhanced nor inhibited the L.E. titer as estimated by the L.E. phenomenon or the complement fixation reaction to nuclear antigens.

### DISCUSSION

Despite recent emphasis on the autoimmune nature of SLE (23, 24) and the demonstration of antinuclear and other "antibodies" in the serum (25), all postulates for an immunogenic origin of this syndrome have not been fulfilled and the etiology still remains obscure. Certainly the presumed antigenic stimulus has not yet been identified and considerable doubt has been cast on the ability

\* Kindly furnished by Dr. Edward Evans, University of Alabama Medical Center, Birmingham, Alabama.



of DNA alone to act as an antigen (26). Even with regard to the antinuclear globulins, in a series of lupus cases, a varied spectrum of serologic reactivity has been shown to occur against whole nuclei, nucleohistone, or DNA. Furthermore, the L.E. cell-producing factor is distinguishable and separate from the antinuclear globulins in serum (25). The reversible lupus syndrome resulting from hydralazine (27, 28), the ill-defined entity of "lupoid" hepatitis (29-31), and cases of isolated rheumatoid arthritis with L.E. factor (32, 33) indicate that multiple stimuli, whether biochemical (enzymatic), viral, or haptenic, acting upon mesenchymal cells may evoke an autoimmune gamma globulin response and the L. E. phenomenon. To this list of nonspecific antigenic stimuli or antibody responses we cautiously submit our present case of cryptococcosis. The serum of this case showed both L.E. factor and a high complement-fixation titer against nucleoprotein. In three other cryptococcal sera studied, L.E. and antinuclear antibodies were absent.

#### SUMMARY

1. Based on a case of primary cryptococcal meningo-encephalitis complicated by a terminal clinical picture of systemic lupus erythematosus with positive L.E. preparations, a study was made of the possible serological relationship between cryptococcosis and SLE. The serum of the patient induced the L.E. phenomenon and reacted in high titer to nucleoprotein.

2. However, blood sera of three additional cases of cryptococcal meningitis failed to induce the L.E. phenomenon or to react with nuclear material or DNA.

3. Intact living cells of *C. neoformans* as well as cryptococcal capsular polysaccharides A, B and C did not give rise to the L.E. phenomenon or react serologically with nuclear material or known L.E. serum.

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## RECURRENCE OF RECTAL CARCINOMA IN THE ABDOMINAL WALL

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It has long been appreciated that accidental tumor seeding at operation might cause recurrence. In 1908, Ryall hypothesized that fragments of tumor borne upon the gloves and instruments of operators might be inoculated into healthy wound areas (1). Bainbridge (2) in 1917 and Greenough (3) in the same year warned that disease might be spread by cutting into malignant tissue. Ewing, in 1933, recommended changing gloves and instruments after biopsying malignant tumors (4). Saphir, in 1936, was able to demonstrate the presence of malignant cells in smears of material from knives used in removal of primary tumors for biopsy (5). Knives with which a malignant tumor had been actually incised invariably showed tumor cells in large numbers either on direct smear or in washings. These cells accepted staining with supravital dyes and were presumably alive. Saphir stated that while most surgeons changed instruments after biopsy the practice was still not universal. In 1946, Brandes and White cited an instance of tumor growth at a paracentesis site in a case of carcinomatosis of the peritoneum, and another at a thoracentesis site in pleural carcinomatosis (6). They also reported an instance in which breast carcinoma was transplanted to a skin donor site in the thigh. Gloves had not been changed between the mastectomy and the taking of the graft. Crile, in 1955, pointed out that there was increasing evidence that incisional biopsies may spread carcinoma and accelerate the course of disease (7). Ackerman and Wheat noted in 1955 that a raw surface is necessary for the successful implantation of carcinoma; the intact skin and mucus membrane are highly resistant (8). They described various types of local recurrence; recurrent carcinoma nodules developing at the margins or ulcerating to the surface of skin grafts applied to areas of tumor excision, carcinoma growing along a needle biopsy tract, and an isolated nodule in a laparotomy incision after oophorectomy. They mention a lag phase before an implant manifests itself, and the tendency to grow as a discrete nodule amenable to surgical excision. Hilberg *et al.*, in 1956, reported on a series of recurrences of carcinoma from diverse anatomic regions in the operative field (9). Studying the correlation of such recurrences with the finding of tumor cells in wound washings at surgery, they found a statistically significant higher local recurrence rate where wound washings were positive or suspicious (9, 23). In 1958, Ship *et al.* showed that when suspensions of free tumor cells are injected into fresh surgical wounds in mice they flourish, producing nodules of tumor tissue. These authors experimented with various lavage solutions finding that 1 per cent formalin was the most effective, offering 85 per cent protection from the survival and growth of the tumor cells (24). Recent studies have been carried out by Thomas and

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Brown, testing the effectiveness of nitrogen mustard, Clorpactin, and other substances for this purpose (10).

Our special concern in this article is with neoplasms of the colon and more especially of the rectum. Recurrence at the site of anastomosis is a well-known phenomenon. Carcinoma fragments dislodged into the lumen of the bowel can be implanted upon the raw cut edge of bowel resulting in such recurrence. Most reports deal with this type of accidental seeding. To cite a few, Goligher *et al.* (11) in 1951 reported on 23 cases of recurrent carcinoma of the rectum after sphincter saving resections. Three were considered fresh primary growths, and five due to inadequate removal of the original tumor. In the remaining 15 the workers felt that the so-called recurrences were most likely surgical implantations. While some of these are open to question, in a goodly number the evidence is highly suggestive. They were able to reduce the the incidence of such recurrences in the latter part of their series by washing the rectal stump with a cytotoxic solution. Cole (12), in 1952, stressed the high incidence of local recurrence at the anastomosis in colon resection which in at least half were due to implantation of carcinoma cells. He pointed out that colon carcinoma seldom travels an appreciable distance in the bowel wall as does stomach carcinoma, and that lymphatic spread distal to the lesion almost never extends a significant distance. When one is two inches beyond a lesion a high recurrence rate due to inadequate excision should not be expected. In 1954, McGrew *et al.* (13) found 16 per cent local recurrences in 55 cases of carcinoma of the colon and rectum following resection. Two-thirds of these were at the suture line. Observations made on specimens removed by standard surgical techniques showed smears from the distal ends positive for malignant cells in 65 per cent of the cases, and from the proximal end in 42 per cent. The average length of the distal segment was 10 cm, of the proximal 21 cm. They felt that surgical manipulation rather than enemata was the significant factor in dislodging the tumor fragments, as in most instances when ligatures were tied above and below the tumor on the average of between 5 and 12 cm from it, smears were negative. They thought the most likely mode of implantation was by the suture carrying the implant into the bowel wall after contact with contaminated mucosa. While they recognized the possibility that implantation might occur merely by contact of the cut edge of bowel with dislodged cells, they thought this less likely as evidenced by the rarity of recurrence in the proximal part of the colon at a colostomy. This rareness of recurrence within a colostomy is mentioned by Goligher *et al.* who found only three such cases in a series of 2000 abdomino-perineal resections at St. Marks' Hospital (11). Black and Kelly in 1955 and many others have also expressed the conviction that the large proportion of instances of local recurrence are due to implantation of viable cells in the anastomosis (14).

While emphasis has been placed on recurrence at the anastomosis, it must not be forgotten that recurrence in the abdominal incision also takes place. Ryall, in 1907, reported four cases of colon carcinoma with recurrence in the abdominal incision and three patients with carcinoma of the rectum operated upon trans-sacraly who recurred in the sacral incision (22). He concluded that carcinoma



cells must have been liberated during manipulation and carried to the incision by the surgeon's hands, instruments, or suture. There were also 18 cases of other varieties of malignancy with recurrence in the surgical incision. Mayo (15), in 1913, referred to a case of stomach carcinoma in which implantation took place into the needle sites of the abdominal incision and Dvorak (16), in 1930, reported a local recurrence in the abdominal wall 13 years after surgery for an ovarian neoplasm. Pomeranz and Garlock published a most interesting study in 1955 (17). They believed that malignant cells could be rubbed off the serosal aspect of neoplasms during manipulation and implanted, having encountered several cases of recurrent tumor nodules in the abdominal wall of patients with colon carcinoma. These recurrences were apparently confined to the abdominal wall. They took smears of the serosal aspect of twenty unselected cases of colon neoplasm as soon as the abdomen was entered and before manipulation. Carcinoma cells were obtained in two (10%). Covering the carcinoma before manipulation was recommended, and a cover was described that combined serosal protection with occlusive ligatures. Ackerman and Wheat in 1955 stated that it is possible to implant tumors of the gastrointestinal tract into the abdominal incision and cited cases of stomach and rectosigmoid carcinoma with such recurrence (8). In 1957, Meadows stated his opinion that transplantation into surgical wounds is much more common than is generally believed and cited five cases that developed wound implants (18). Boreham, in 1958, discussed implantation from the peritoneal surface of a growth onto the abdominal wall (19). He felt it was uncommon, but referred to six cases of colon carcinoma in which contamination of the wound from the peritoneal surface of the growth had probably taken place.

In rectal carcinoma treated by abdomino-perineal resection, recurrence in the abdominal wound is rare. Mayo, in 1913, described such a recurrence (15). His patient underwent a two-stage procedure for carcinoma of the rectum. At first a double-barreled colostomy was made in a left rectus wound. The distal bowel was cleansed by enemas and 12 days later the rectum and sigmoid were excised transsacally, the sigmoid being transected and closed six inches proximal to the tumor. Seven weeks later recurrent carcinoma was noted in the abdominal wall at the inner edge of the colostomy stoma. He felt the implant was due to engrafting of tumor dislodged by operative manipulation. He apparently did not think the enemas a factor of significance. The secondary growth was excised with apparent cure.

Another such case was recently described by Sonneland in 1960 (20). The remarkable feature of this case was a 17 year latent period between the original operation and the recurrence in the incision. The patient was a woman who was first operated upon by Dr. Charles W. Mayo in 1939 when she was 57 years old. At that time a combined abdomino-perineal resection was performed for adenocarcinoma of the rectum situated six inches from the anus. No lymph node involvement was seen and the peritoneum and liver were free of tumor. In 1944, carcinoma of the cervix was found and radiotherapy administered. A later local recurrence of the cervical tumor was retreated with radiotherapy. In 1954 papil-

lary transitional cell carcinoma arose in the urinary bladder. This was treated by transurethral excision and fulguration. In 1956 the patient developed acute small bowel obstruction and at laparotomy two zones of jejunal postradiation constriction were noted. Fifteen centimeters of bowel were resected. At that time exploration of the abdomen was negative for tumor. Immediately following the latter operation a 1 cm mucoid nodule was noted adjacent to the colostomy stoma. Biopsy was interpreted as adenocarcinoma. A wedge resection of the abdominal wall containing the colostomy was performed and a new colostomy was created. On pathological examination the tumor cells were seen to be located in the fibrous tissue of the old suture line at the junction of the skin and colostomy mucosa. No lymphoid elements were noted and the tumor was not contiguous with the colostomy mucosa. The histology was similar to that of the original rectal carcinoma. When last seen in 1959 the patient showed no evidence of recurrence.

Other cases of recurrence in the abdominal wall adjacent to a colostomy, such as two reported by Boreham following perineo-abdominal resection, differ in that the rectal carcinoma was drawn through the colostomy incision (19). He also refers to abdominal wall recurrence around the colostomy in two cases following Mikulicz resection, in one case of familial polyposis where another primary was likely, and in two cases where the growth was very extensive locally and the excision was not considered radical enough.

The following is the report of a case operated upon by us (E.E.J.):

J.P., The Mount Sinai Hospital #130765, was a 74 year old man first admitted on July 25, 1959 complaining of urgent and frequent bowel movements for six weeks. Of late, the frequency approached twenty times daily and the movements contained dark red blood. Upon rectal examination a hard flat, anteriorly situated mass was palpable two inches from the anus. Physical examination was otherwise negative. At sigmoidoscopy, at 7 cm, a 6 x 6 cm flat tumor was seen on the anterior rectal wall. Biopsy demonstrated adenocarcinoma.

On July 29, 1959 abdomino-perineal resection of the rectum and sigmoid colon was performed. A large tumor growing through all layers of the rectal wall and infiltrating the *cul-de-sac* peritoneum was found. The pre-aortic nodes, the liver, and remainder of the peritoneum were grossly free of tumor. The proximal sigmoid was the resection level selected. Lymph nodes from the mesentery at this level were found uninvolved on frozen section. The sigmoid and rectum were mobilized from above, the sigmoid divided and the proximal end brought out through the main wound as a colostomy. The distal bowel containing the carcinoma was buried in the pelvis and removed transperineally.

The resected specimen measured 39 cm. Seven cm from the anus there was a large flat tumor measuring 6 x 6 cm. The tumor replaced all layers of the rectal wall, had an ulcerated center, and puckered the external surface. Proximal to this a small pedunculated polyp measuring 1 cm was found and 12 cm more proximally was a second 1.5 cm polyp on a 4 cm stalk. The microscopic report was infiltrating adenocarcinoma with five involved lymph nodes. The most proximal lymph nodes were free. The most proximal polyp showed focal carcinomatous change.

The patient enjoyed an uneventful postoperative course and his abdominal wound healed per primam with a normal appearing and normally functioning colostomy.

On July 12, 1960, during a routine follow-up visit, examination of the colostomy stoma disclosed heaped-up tissue at its lower margin. This resembled dirty, gray, unusually firm granulation tissue (Fig. 1). Biopsy proved this to be recurrent carcinoma. Upon palpation there was a sense of a walnut-sized mass in the abdominal wall beneath this area.

On July 26, 1960 en bloc resection was performed of a 20 x 5 centimeter ellipse of abdominal wall, the circumscribed colostomy and recurrence, the remaining left colon and splenic flexure, and their mesentery. A new distal transverse colostomy was formed. The neoplasm extended for only a short distance below the abdominal wall. The mesentery throughout was grossly free of infiltration or involved lymph nodes. Careful reexploration of the abdominal cavity revealed no other evidence of metastases.

The resected colon was 24 centimeters long. On section the abdominal wall mass was firm



FIG. 1. Photograph of colostomy showing recurrent carcinoma at lower angle.

and grayish-white. Microscopically, it showed infiltrating adenocarcinoma. The involvement extended up to but not into the colonic segment. The edge of resected skin was free of carcinoma and lymph nodes were not involved.

The postoperative course was again uneventful. The patient was discharged in August 1960 after the wound had healed primarily and the colostomy had resumed satisfactory function. At a follow-up visit on March 20, 1961 the colostomy was functioning well and there was no evidence of recurrence.

#### DISCUSSION

The principles for the prevention of implantation of carcinoma cells at surgery have been long understood. As early as 1909, Babler stated, "Successful carcinoma surgery signifies the strictest asepsis, the most gentle handling of the

growth, the avoidance of cutting and tearing into the carcinomatous growth and diseased tissue, the excision of all diseased lymph glands and channels, wide excision of the carcinomatous tissue and the destruction of cancer cells which may have been liberated and found their way into the operative wound in spite of all precautions" (21).

Unfortunately, in practice it is not always possible to apply these principles with the completeness and promptness one would desire. In surgery for colon carcinoma three preliminary measures would be required prior to manipulation to prevent dissemination: viz. a) ligation of the blood supply and accompanying lymphatic channels, b) occlusion of the bowel lumen by ligatures above and below the tumor mass to contain intraluminal fragments, c) covering the external surface of the tumor with impervious material.

In the case of low-lying colonic lesions, the surgeon can neither ligate the bowel below the tumor nor avoid handling the bare external wall of the bowel in mobilizing it. Additional precautionary measures may be instituted, such as carefully walling off the operative field, frequent change of gloves and instruments, and irrigation of the operative site and rectal stump with various cytotoxic solutions (*e.g.* half-strength Dakin's solution, 0.5% Clorpaetin xcb, 1:500 perchloride of mercury, or nitrogen mustard). At best only an approximation of the described ideal can be attained.

Despite these considerations, abdominal wall recurrence is uncommon following colonic surgery and rare following rectal surgery, although the data regarding such recurrence are of necessity incomplete, as most cases of recurrent carcinoma are not reported. In the case presented, the location of the tumor recurrence at the mesenteric angle of the colostomy at first led to the suspicion that the new growth had arisen from involved mesenteric lymph nodes that were not detected at the original surgery. This hypothesis was disproved by the findings. Recurrence must have occurred as the result of free implants dislodged in the process of mobilizing the rectum from the pelvis. It will be recalled that the tumor replaced all layers of the rectal wall, puckering its external surface and infiltrating the *cul-de-sac* peritoneum. The observed fact that such recurrences are rarely seen is either indicative of the efficacy of the described precautions or evidence that the defensive mechanisms of the host can usually destroy dislodged cancer cells.

#### SUMMARY

1. The accidental seeding of malignant cells during surgical procedures as a cause of recurrence is discussed with particular reference to colon and rectal carcinoma.
2. The role of implantation in recurrence at the site of anastomosis in resected colon carcinoma is reviewed.
3. Implantation as the cause of recurrence of colon and rectal carcinoma in the abdominal incision is also discussed.
4. A case of recurrence of rectal carcinoma in the abdominal wall following abdomino-perineal resection is presented.
5. The principles for the prevention of such recurrences are enumerated.



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# *Clinico-Pathological Conference*

## EPIGASTRIC DISTRESS, PLEURAL EFFUSION, FEVER AND GASTROINTESTINAL BLEEDING

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A 58 year old business man was admitted to The Mount Sinai Hospital because of nausea of one month's duration. He had been working unusually hard for three years and felt that he had worn himself out. He noted a decrease in libido, depressions, tiredness, and crying spells for about four months. For one month he experienced high epigastric discomfort, nausea and vomiting, which were relieved by sitting up or taking antacids. He lost ten pounds during this time. Past history and review of symptoms were noncontributory.

He was obese, had a ruddy complexion and a slow affect. His temperature was 102° but other vital signs were normal. He had bilateral submaxillary gland enlargement and a small right supraclavicular lymph node. The heart and lungs were normal except for slight emphysema. The abdomen was obese and the liver was percussed two fingers below the right costal margin. No edge or nodules were felt. No other organs, masses or tenderness were detected. The skeletal and neuromuscular systems were normal. Rectal examination was negative.

Urinalysis was initially normal, but later, occasional glycosuria was noted. Hemoglobin was 13.3 Gm% and, despite many transfusions, this dropped gradually to 7.7 Gm% before death. The white blood count was 3300/mm<sup>3</sup> with 88% segmental leukocytes, 3% band forms, 8% lymphocytes and 1% monocytes. The white blood count never exceeded 4300/mm<sup>3</sup> and the lymphocytes were never above 18%. As a result of therapy, counts as low as 400/mm<sup>3</sup> were obtained but such depression was only transitory. Reticulocyte counts varied between 1-2%. Platelet counts were between 125,000 and 200,000/mm<sup>3</sup>. Bone marrow study showed only normal cells in normal numbers and was called non-diagnostic. The sedimentation rate was 57 mm/hr. Stool guaiac examinations were negative until just before death. No free acid was detected in the stomach after histamine stimulation. A tuberculin test was negative. The BUN was 23 mg%, blood sugar 182 and 151 mg% and serum cholesterol 125 and 218 mg% with 85 and 180 mg% esterified respectively. The serum bilirubin was 0.6 mg% with 0.3 mg% conjugated. The serum alkaline phosphatase was 13.7 KA units. Serum calcium was 8.9 mg% and phosphorus 3.5 mg%. Serum albumin was 3.1 Gm% and globulin 2.4 Gm%. Febrile and heterophile agglutinins, LE preparations, and numerous blood cultures were negative. Stool cultures grew *E. coli* and *A. aerogenes* enterococci and, in one specimen, *Salmonella anatum* (group E). An electrocardiogram revealed low voltage of QRS complexes and T waves.

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Chest x-ray demonstrated a right pleural effusion with prominent markings in this area but no discrete infiltrations. A barium meal showed a small hiatus hernia, poorly defined and somewhat shallow gastric mucosal folds, widening of the duodenal loop, and thickening of the mucosal folds of the duodenum and proximal jejunum. There was no evidence of undue distension of the small bowel. The excretory urogram was normal and the kidneys were normal in size and location. The spleen was somewhat enlarged. The bones were normal. After thoracentesis, the pleural effusion was less but an irregular density was noted for the first time in the right second interspace. This infiltration was present but slightly smaller after two weeks of observation.

In the hospital the patient's course was downhill with fever and weight loss. A thoracentesis was performed on the fourth hospital day and yielded a sterile serous fluid with a protein content of 4.2 Gm% and a cell count of 80/mm<sup>3</sup> (2 segmented leukocytes, 50 lymphocytes, 44 large mononuclear cells, and 4 cells in mitosis). No tumor cells were seen on smear or in a cell block. Because the clinical picture seemed to suggest a lymphoma, the patient was given a course of nitrogen mustard and steroid therapy. This resulted in temporary improvement only, in fever, and in agranulocytosis with oral ulcers. The white blood count gradually rose but three weeks after the mustard was given and while the patient was still on steroids and antibiotics, he developed hematemesis and melena. Fever persisted with temperatures of 101 to 103°. The patient lost 16 pounds in the hospital and appeared to lose considerable strength. The gastrointestinal bleeding continued intermittently for a week and, despite blood replacement, the patient expired on the 46th hospital day.

*Dr. Richard H. Marshak:*\* I would like to describe the x-rays first and then the protocol. This was an extremely interesting upper gastrointestinal series. There was a small sliding hiatus hernia which was of no clinical significance. The stomach was cascade in type and completely distensible on its lesser curvature aspect. No organic filling defects were seen within the stomach. On the greater curvature aspect of the stomach, there was a coarse nodularity. In addition there was evidence of extrinsic pressure in this region. Usually in this region, on the greater curvature aspects of the stomach, one sees enlarged folds. This was completely replaced by nodularity, infiltration and evidence of a mass. Inferiorly there was again evidence that a mass was pressing on the small bowel in the region of the ligament of Treitz. As one proceeded distally, the duodenal bulb appeared normal but again the duodenal loop seemed to be widened. There was coarsening of the folds throughout the entire extent of the duodenal loop. No ulcerations and no evidence of any intrinsic tumor mass were seen in this region.

The papilla of Vater was well-outlined and appeared to be within normal limits. Immediately above the papilla there was an interesting scalloped indentation. This was a nodule which from the roentgen point of view we must consider to have been a submucosal infiltration. Most frequently it is seen with

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malignant process that invades the submucosa without necessarily going into the mucosa. The folds were coarsened throughout the duodenal loop.

Although the spleen was not palpated clinically, there definitely appeared to be some enlargement of the organ. The normal vertical fold of the duodenum in the region of the ligament of Treitz was replaced by an almost arc-like configuration, again suggestive of a mass in this region.

The most common cause of a mass in the region of the tail of the pancreas is a carcinoma. On the other hand, we must explain that in addition to the mass, there was widening of the duodenal loop as well. Carcinomas of the pancreas can be very large. They also can be multicentric and although the mass in this particular region was probably in the body and tail of the pancreas, there is no reason why there cannot be multiple foci in the region of the head of the pancreas. This particular patient was not jaundiced but jaundice does not occur in from 10 to 15 per cent of the patients with carcinoma even involving the head of the pancreas. Since the main lesion here appeared to be in the body and tail of the pancreas, it is readily understandable why this patient did not have any jaundice.

Because of the large size of the lesion, however, other possibilities must be considered. It is of interest that there are very few systemic lesions that will give an enlargement of the pancreas itself. Enlargement is seen in mumps and Boeck's sarcoid, but an enlarged pancreas for any other reason is usually due to some pathology with the pancreas.

I cannot completely exclude the possibility of lymphosarcoma. In a review of 67 cases of lymphosarcoma of the small bowel that we had at this hospital, however, only one patient displayed an isolated group of lymph nodes in the pancreatic area. In this particular case the lymph nodes were so large that they also caused some rotation of the kidneys. It is difficult for me to understand how a lymphosarcoma could be so huge in this region without in some way distorting the kidneys or the ureters, which appear to be normal. Since the main mass appears to be on the left, in the body and tail of the pancreas, one should note that the left kidney was normal in position, with no mass above it. To favor lymphosarcoma, one would like to see something else in other loops of the small bowel. An entire small bowel series is not available but as far as one can go, the remainder of the small bowel appears to be normal. The abnormal findings appear to stop abruptly immediately distal to the ligament of Treitz.

In the chest there was an effusion at the right base. It is true that a patient who has a carcinoma of the body and tail of the pancreas should have the effusion primarily at the left base with metastatic involvement. On the other hand, effusions are frequently found with lymphosarcomas as well. After the fluid was tapped, no abnormality was present in the right lung field, indicating that there was no infarction or pneumonia. There did appear terminally, however, a small nodule in the right subclavicular region.

I would like to go to the protocol for a moment and see whether it would substantiate the diagnosis of a carcinoma of the pancreas or if the findings favor a lymphosarcoma.



The clinical findings were of a patient who lost a considerable amount of weight. There were crying spells for about four months. It is well known that psychiatric findings have been frequently reported with carcinoma of the pancreas, but I am sure this will not be an overwhelming factor in the diagnosis.

The temperature was 102° which is more indicative of a lymphoblastoma. If this patient had a carcinoma, it was huge. A patient with a huge carcinoma and metastases can also have fever. Fever does not necessarily have to be on the basis of a lymphosarcoma although carcinomas of the pancreas usually are not necrotic. With a slightly elevated alkaline phosphatase and slightly enlarged liver, the patient might have had metastases to the liver as well.

The next interesting finding is glycosuria. If this was in the absence of any drug, it is an important observation in a patient who has a carcinoma of the body and tail of the pancreas. It is true that lymphosarcoma can involve the pancreas. I understand that glycosuria is rather unusual except at the time of death, but it would be significant in the diagnosis of a malignancy in the pancreas.

The next important finding was the blood count. This patient had a considerable anemia, despite multiple transfusions. He also had a very low white count with reduced platelets which would be more typical of lymphosarcoma. Since the lesion was primarily in the region of the body and tail of the pancreas, it is conceivable that there was a splenic vein thrombosis. The splenic vein thrombosis would cause an enlarged spleen and the hematologic findings associated with hypersplenism could explain the low white count. I have been able to find very few cases of carcinoma of the pancreas with this particular hematologic picture, but it has been described with splenic vein thrombosis. In view of the tremendous size of the lesion, it is possible that there was involvement of the vessels in this region.

The fact that salmonella anatum was cultured in the stool is of consequence. Cases have been reported where the lymph nodes in the abdomen became huge as a result of salmonella infection. This can be associated with a low white count, but I am sure that if this was an abscess due to salmonella, the diaphragm would not appear normal, there would be no transudate in the pleura and it would have been an infection with subphrenic abscess. We have no findings compatible with a subphrenic abscess and I understand that the diaphragm moved readily.

Immediately prior to death, the patient began to bleed. The bleeding could have been due to a variety of reasons, but perhaps the multiple implants from a carcinoma of the pancreas eroded into the intestinal tract. I have seen several cases where they appeared as duodenal ulcers with exsanguination. After nitrogen mustard therapy, it is possible that part of the tumor sloughs with erosion of the mucosa, also producing the hemorrhage. Patients have developed granulocytopenia as well as thrombocytopenia which caused severe bleeding.

Another lesion that should be mentioned is metastatic nodes in the region of the pancreas. In view of the effusion at the right base, carcinoma of the lung must be considered, but I have not seen metastasis to this area. These tumors

usually metastasize to the lumbar region. With the seminomas I have seen, the nodes are usually enlarged in the pelvis, and then proceed upward. They do not localize in this particular region.

In conclusion, because the lesion appears to be exquisitely demarcated by the duodenal loop and the ligament of Treitz, and resides in the pancreas, I think the most likely diagnosis would be a lesion of the pancreas itself. A carcinoma of the body and tail of the pancreas also involving the head would be my first diagnosis. I cannot exclude the possibility of a lymphosarcoma, but if this were a lymphosarcoma, I would like to have seen more involvement, other abdominal masses, and further evidence of this particular disease.

*Dr. Hans Popper:*\* What was the alteration of the small intestine, if any?

*Dr. Marshak:* There were two scalloped defects which appear to be tumor tissue indenting the small bowel. I do not see discrete ulceration at this site. I would suspect, since this patient had nitrogen mustard, multiple areas could very easily have eroded into the small intestine and they are around this particular region.

*Dr. Burrill B. Crohn:*† Was there a palpable mass in the abdomen?

*Dr. Marshak:* There was no palpable mass and no free fluid in the abdomen. Another lesion I wanted to mention was an exogastric myosarcoma. If this was such a tumor, the only way I can explain the drop in hemoglobin would be hemorrhage into the sarcoma itself. If this occurs, usually the outline is exquisitely smooth, such as in a pancreatic cyst. In this case it is one of nodularity and indentation, which is seen more often with an infiltrating lesion like a carcinoma or possibly a lymphosarcoma.

*Dr. Crohn:* I have seen a mass of nodes in the area under discussion. In one instance it was tuberculous and in another case it was nonspecific lymphadenitis. In each instance there was obstruction of the jejunum at the fossa of Treitz with intense vomiting, so that the predominant picture was one of intestinal involvement rather than one of pancreatic disease.

The point that Dr. Marshak makes and that I also raise is if there is any disturbance of glucose metabolism. A mass in the pancreas, is often associated with a disturbance in sugar metabolism. Of course, fever in carcinoma of the pancreas is not usual. Pain may be intense. Many cases begin with a clinical picture of psychoneurosis. Only later do the pancreatic symptoms become evident. Polycystic disease of the pancreas has to be considered with large intra-abdominal masses of this type, but it certainly looks like a neoplasm.

*Dr. Popper:* How would you feel about the rapidly increasing anemia, which apparently has dropped from virtually normal to 7.7 grams in 46 days?

*Dr. Crohn:* When the papilla of Vater is involved by carcinoma, a secondary ulceration can take place. Gross hemorrhage in carcinoma of the pancreas involving the head is not unusual.

*Dr. Marshak:* The disturbing factor in the diagnosis of a carcinoma of the

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pancreas is the initial normal hemoglobin followed by sudden onset of anemia without blood in the stools. Nevertheless, I have seen a sudden drop in hemoglobin when hemorrhage occurred into a cyst.

*Dr. Crohn:* Dr. Osler made the point that there is never a palpable spleen in intra-abdominal carcinoma. Then, later, he made the exception for thrombosis of the splenic vein.

*Dr. Bernard S. Wolf:*\* We thought that the small bowel distal to the ligament of Treitz was unusually far anteriorly. We had the feeling that this mass was more extensive than simply in the region of the head of the pancreas and that it probably extended into the root of the mesentery. The bowel was displaced forward as a result. I did not see enough displacement of the upper portion of the posterior aspect of the stomach to explain a large lesion in the region of the body and tail.

*Dr. Marshak:* The other diagnosis is lymphosarcoma in that area, which would explain the anemia and other findings. I have not seen a lymphosarcoma like this, but I guess it can occur.

*Dr. Popper:* We will start with the intestine, as long as Dr. Marshak rightly put it in the foreground. The jejunum immediately following the ligament of Treitz contained prominent nodular areas and between them the mucosa was in part denuded. The muscularis was not thickened and in no way was involved. Actually very little submucosal involvement was present. The mucosa bulged forward in the form of small polyps. They were pseudopolyps which were inflammatory in nature. A large number of lymphoid cells made up the bulk of each "polyp" and they really consisted to the greatest extent, of lymph follicles with some fibrosis in the center and some glands around them (Fig. 1). A little further down in the jejunum, we saw edema with irregular thickening of the mucosal folds with areas which were depressed but without ulceration. The infiltration extended into the muscularis and into the mesentery. At the insertion of the mesentery, accumulation of cellular elements was noted but these were not carcinomatous in nature. Microscopically, the mucosa was not ulcerated but there was infiltration and a defect of the epithelial lining which was most probably a postmortal effect. Extensive infiltration of the submucosa produced thickening and irregularity of the folds and some distortion of the mucosa. Many cells were seen between the glands in the mucosa. The nature of these cells was difficult to analyse. The lamina propria of the intestine contained a great variety of cells. About twenty centimeters into the jejunum, we saw infiltration of all layers extending through the muscularis without fibrosis. The infiltrating cell was eosinophilic, had a large nucleus and was an atypical reticulum cell or lymphoblastic type of cell, better described as a stem cell because of the large nucleus. Extensive phagocytosis and phagocytic giant cells were part of the lesion. In this patient under nitrogen mustard treatment, probably some of the phagocytosis and megakaryocytosis was a result of the drug therapy. The cell itself, which was responsible for infiltration of the mucosa

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and infiltration of the muscularis and submucosa, was then a lymphoblastic or reticulum cell. Nowhere was fibrosis seen, despite the irregularities, and we were in no way inclined to consider the lesion Hodgkin's disease, but rather, a very malignant type of a lymphoblastoma. This did not involve lymph nodes,

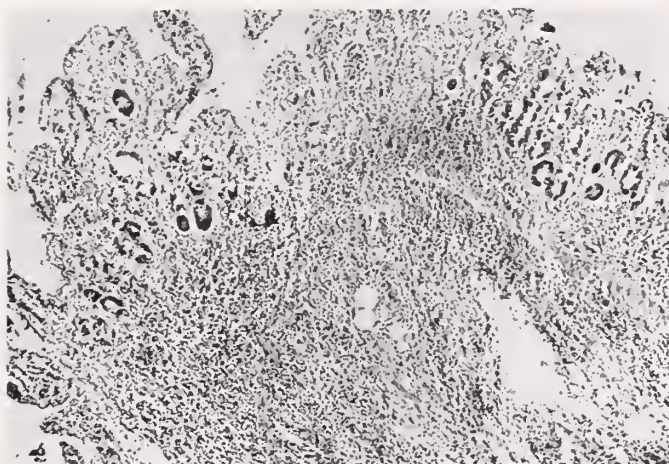


FIG. 1. Polyp-like thickening of villi in jejunum with cellular infiltration of all layers and lymph follicle formation. (H & E  $\times 40$ )

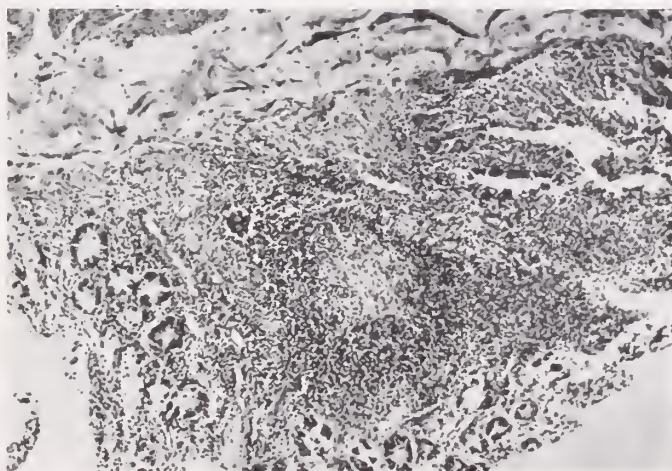


FIG. 2. Enlargement of lymph follicle in colon with mucosal infiltration. (H & E  $\times 40$ )

but actually, the mesentery. The entire root of the mesentery outside of lymph nodes showed diffuse infiltration by the same type of cells. In the colon, areas were seen where there were projecting lymph follicles with infiltration of the mucosa (Fig. 2). The mesenteric nodes were distinctly enlarged but not matted together (Fig. 3). In the lymph nodes, the architecture was completely obscured and the capsule was extensively invaded. The cells were of the same type as in



the intestine, i.e. reticulum form of lymphosarcoma. Some of them were formed giant cells and many of them were undergoing karyorrhexis. The breakdown products were taken up by other cells to give us the element of phagocytosis (Fig. 4). The phagocytosis sometimes was predominant but in other areas the

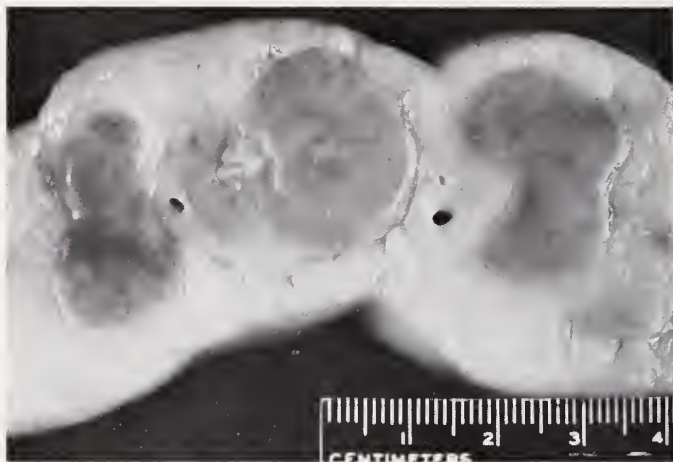


FIG. 3. Large discrete lymph nodes in thickened mesentery.

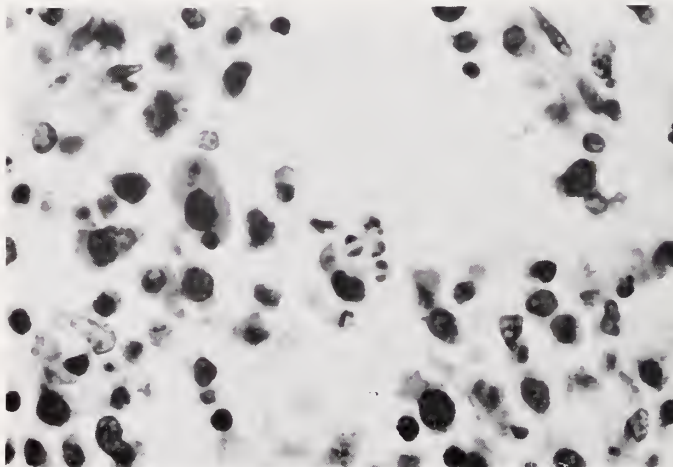


FIG. 4. Basophilic and eosinophilic cells in lymph node showing evidence of phagocytosis (arrow). (H & E  $\times 640$ )

cells resembled plasma cells and had the plasma cell type of nuclei. We had a somewhat polymorphic picture but even with giant cell formation, nowhere did we see evidence of fibrosis, which excluded Hodgkin's disease. The giant cells were part of this lymphoblastic lesion. A feature which was important in the understanding of the case was extensive invasion of blood vessels by cells which showed the effects of therapy. The spleen was large, weighing 600 grams, and was

18 centimeters in length. On the cut surface no nodules were seen and the architecture was accentuated. What remained of the lymph follicles appeared large and cellular. In the red pulp, the lymphoblastic cells, very polymorphic in type, were seen, preserving the architecture in principle. In addition, extensive iron deposition or hemosiderosis was present, resulting no doubt from the numerous blood transfusions, as well as the hematologic disturbances, from which the patient suffered. Phagocytosis was reflected in the PAS positive staining of many of the cells. The bone marrow showed relatively little change. Small areas of hemorrhage were noted, probably an effect of therapy. We saw increased megakaryocytes but although we knew that lymphoblastic spread was throughout the body, we had great difficulty on examination of the marrow, as did the hematologists, to be sure that we were dealing with something more than a reaction to therapy. Some reticulum cells were seen but these were not definitely tumorous in character. The liver was also large, weighing about 2000 grams. The architecture of the liver was entirely preserved. Centrilobular necrosis with hemorrhage was present, probably due to passive congestion from which the patient suffered just prior to death. The liver was involved in the lymphoblastic process to a relatively mild degree. We had to look extensively to find areas where lymphoblasts could be seen. The reticuloendothelial cells were quite extensively activated. We have to assume that the enlargement of the liver was not the result of the involvement by the lymphoblastoma, but rather, from reticuloendothelial proliferation which we also saw in the spleen. Isolated lymphoblastic cells were found in some of the portal tracts. In contrast to Hodgkin's disease, these cells spare the bile ducts and therefore, there was no jaundice or any bile stasis even in the few areas where infiltration was rather extensive. Quite a few glycogen nuclei were present suggesting diabetes. Hemosiderosis, previously mentioned, was quite clearly seen in the liver with iron accumulated in the proliferated reticuloendothelial cells as well as in the parenchymal liver cells.

Dr. Marshak has quite rightly pointed to the importance of the pancreas in this case. He stated that we were dealing with diabetes. We saw diffuse infiltration by lymphoblastic elements throughout the peripancreatic tissue but no lymph node involvement. Microscopically, in some areas, the cells seemed to invade the pancreas producing lymphoblastic type of pancreatitis which obviously accounted for the diabetic lesion. The stomach was less involved. Some infiltration was present in the submucosa and some sparsely scattered in the lamina propria. The esophagus, however, had extensive areas of necrosis with an almost undermining type of ulceration extending down from the middle half. We also saw many small but deep mucosal ulcerations and some destruction of the muscular layer. Microscopically, we recognized hemorrhage, destruction of vessels, and cellular infiltration. Actually, we were dealing with two types of cells: some lymphoblastic cells and many segmented leukocytes. An infection of the esophagus was superimposed on lymphoblastic infiltration. We looked for fungi, but attempts to identify them with fungus stains did not succeed. In the spleen, however, we found *Candida albicans* as well as *B. coli*.

In the lung two types of lesions were seen. There was a diffuse thickening of the pleura and a large area of infiltration which was lymphoblastic. This was accompanied by a pleural effusion due to the lymphoblastic infiltration. In addition, the diaphragm on both pleural and peritoneal surfaces showed infiltration by lymphoblastic tissue. In the lung itself, there were small abscess cavities. We saw a large number of giant cells but these were not tumor giant cells. They were the result of a fungal infection from which *Candida albicans* was cultured. The patient had an extensive fungal infection of the lung.

The heart grossly did not appear changed. Microscopically, however, there was infiltration by lymphoblastic cells, almost as in leukemia (Fig. 5). In addition was found striking activation of the endothelium. This endothelial proliferation was a manifestation of sepsis. In the epicardium there was soft tissue infiltration. In the soft tissue, spread of lymphoblastic tumor elements

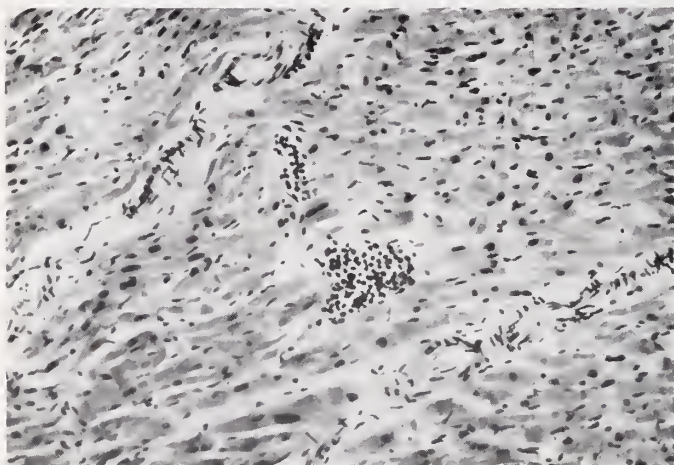


FIG. 5. Lymphoblastic infiltration of myocardium. (H & E  $\times 120$ )

was noted. This also involved parts of the pericardium and some pericardial effusion was found at the time of death.

The thyroid showed involutionary changes, but in addition, lymphoblastic cells had accumulated. The kidney was involved by the same tumor tissue in the form of hemorrhagic infiltrations as well as nodules. Here we again saw the very characteristic feature of the lymphoblastic tissue which extended by infiltration and dissemination but left the original structures intact. Even at the time when this tissue was disintegrating under the effect of chemotherapy, sufficient intact renal structures remained to explain the lack of any significant azotemia.

Let me summarize this case. First, we have to analyze cytologically the types of lymphoma (1): there is the undifferentiated group with a poor prognosis, a moderately differentiated one with a better prognosis, and a fairly well-differentiated one with many years of survival. The last is giant follicular lymphoblastoma. The moderately differentiated one is lymphocytic lymphosarcoma

and Hodgkin's granuloma, which is really a type of lymphogranulomatosis with a mixture of a large number of cells. This is a German term that appeals to me because it describes the lymphatic cells as well as the granulomatous elements. Finally there is the undifferentiated type which includes Hodgkin's sarcoma, lymphoblastoma, and reticulum cell sarcoma which some call stem cell sarcoma and others call karyocytic because of evidence of phagocytosis.

I have given the older classical subdivision. A modern classification on a functional basis is advocated by some in accordance with functional nomenclature.

Such a classification is based on the description of cells by functional methods rather than on the cytologic characteristics. One cell is the reticulum cell which we are discussing. It is a reticulum supporting cell and is fibroblastic. Next, we have basophilic blast cells of the type which forms protein but does not secrete it. The protein-secreting type of cell is the plasma cell. Related to these are the lymphocytic cells. Finally, the cell which was involved in this case is the monocytic or histiocytic cell which is active in phagocytosis and is the precursor of the basophilic activated reticulum cell. I am not sure whether the monocytic feature of phagocytosis, which was so extensive, may not have been elicited by therapy and whether this is not a tumor cell of the premature basophilic reticulum cell.

We have, therefore, a lymphoblastoma of the reticulum cell or basophilic cell type. Now the question of distribution arises. Several types of distribution are possible (2-6). The first is local which, for instance, may occur in the intestine. In these cases a localized ulcer, a fungating lesion or uniform thickening is present by invasion from the lymph nodes. All these have variable prognoses. The second type is the leukemic form. Neither form is present in this case; this was not lymphoblastoma of the intestine. The lesion here was diffuse lymphosarcomatosis with involvement of the intestinal and mesenteric nodes, progressing into the intestine with ulceration. It was present in the spleen and in the pancreas resulting in low calcium in the serum and in diabetic manifestations. It also involved the diaphragm, the pleura and the pericardium. Spread occurred to the kidneys, liver, myocardium, thyroid, bladder and to the prostate.

There were several reasons, therefore, for the clinical manifestations. Reticulum cell lymphosarcomatosis disseminates rapidly and causes malaise, weight loss, fever, anemia and leukopenia. There was drug induced karyorrhexis and phagocytosis which may have been responsible for hemorrhage and granulocytopenia. Enhanced by drugs, diabetes and steroids, *B. coli*, *Candida* sepsis, and pneumonia developed; the sepsis accounted in part for the hepatosplenomegaly. Gastrointestinal hemorrhage occurred from two areas in which sarcoma and infection were intermixed—the small intestinal ulcerations and possibly the esophagus. Finally, cardiac failure developed as the result of myocardial involvement.

In closing, this was a lymphoma involving the small intestine but an unusual type of lesion because it was not a primary lymphoma of the small intestine. It was diffuse lymphosarcomatosis involving the soft tissue, possibly starting in



the mesenteric nodes and spreading by extension into the intestine, into the surrounding tissue and by the hematogenous route to other organs. The diffuse nature of the lesion accounts for the very rapid course.

*Dr. Marshak:* We do not see this miliary form of lymphosarcoma with these tiny nodules and small alterations in the x-ray. Even in retrospect, we looked for ulcerations and none were seen. All I saw were the tumor nodules which were probably the large lymph nodes implanted in the region of the ligament of Treitz and the second portion of the duodenum. If I had seen any more distally, then I would have made the correct diagnosis. Unfortunately the large tumor nodules were all in the region of the head of the pancreas. Most of the lymphosarcoma we can recognize is of a more gross form.

*Final Diagnosis:*

1. RETICULUM CELL LYMPHOSARCOMATOSIS INVOLVING MESENTERIC NODES, INTESTINE, PANCREAS, SPLEEN, KIDNEYS, LIVER, MYOCARDIUM, THYROID, BLADDER AND PROSTATE.
2. CANDIDA ALBICANS AND B. COLI PNEUMONIA AND SEPSIS.

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# *Radiological Notes*

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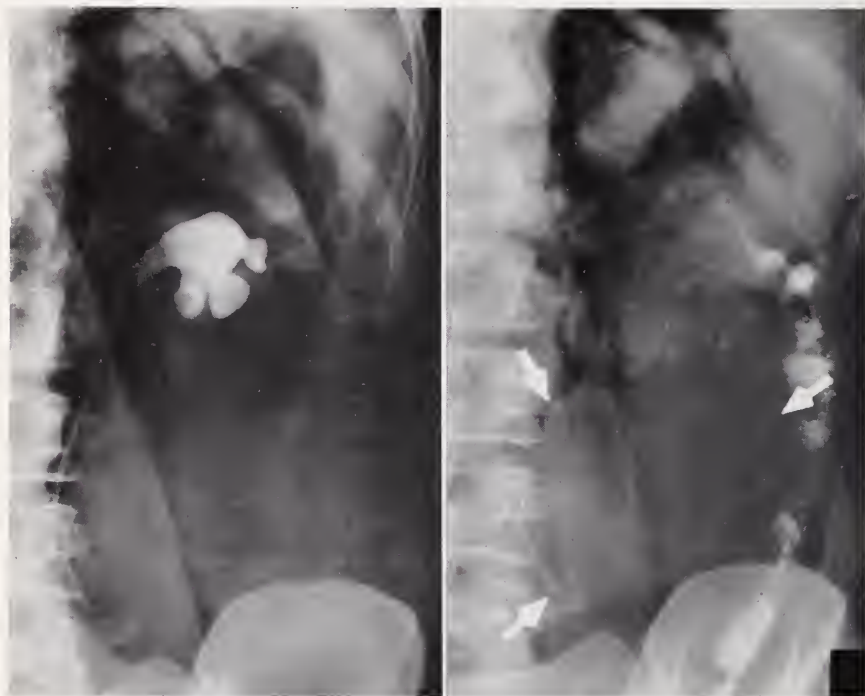
## CASE NO. 150

This was the first admission of a 38 year old female for "observation." The patient was in the habit of having a physical check-up every one or two years. Two weeks before admission, during such an examination, a "dropped left



Case 150, Fig. 1. Preliminary film of the abdomen shows a peculiar configuration to the lower pole of the left kidney. Between arrows A and B, the lower pole is flattened and its outline lost as a result of a lucent zone which extends superiorly into the parenchyma of the kidney. In addition, below and continuous with this area, the left flank is unusually lucent (arrow C) without any evidence of gas-containing loops of bowel.

kidney" was found. In actual fact, however, the referring physician had palpated a mass in the left flank. Past history was entirely negative. Pertinent physical findings were confined to the abdomen. The right kidney was not palpable. In the left upper quadrant, however, there was a fixed ballotable, smooth mass which was not tender. Hemoglobin was 12.9 Gm, white blood count 8,000 with



Case 150, Fig. 2. Left retrograde ureteropyelogram and simultaneous retrorectal air insufflation shows the lower half of the double pelvis which seems to droop inferiorly. The lower pole of the left kidney is effaced. The left ureter is moderately displaced towards the midline. A discrete soft tissue mass density is not clearly evident.

Case 150, Fig. 3. Film taken one day after retrorectal air insufflation shows residual gas around the kidney. A globular mass is faintly evident (arrows) outlined in places by gas or a thin rim of water density tissue (capsule?). This finding indicates the lipomatous character of the tumor. (Barium in the left side of the colon was the residual of a previous barium enema.)

a normal differential count. Intravenous pyelography prior to admission demonstrated a double pelvis in the left kidney. Left retrograde ureteropyelogram was done simultaneously with retrorectal air insufflation. The preliminary film of the abdomen demonstrated a broadening of the lower pole of the left kidney; a segment of its lower contour was missing (Fig. 1). In this area, instead of a soft tissue contour of kidney or mass outlined against perirenal fat, the entire region extending upwards into the kidney and downwards into the flank for several

inches appeared unusually lucent. The retrorectal air insufflation (Figs. 2, 3) confirmed the presence of a discrete globular mass above the crest of the left ilium which was continuous with the lower pole of the left kidney. It was surprising on this examination to note the excessive lucency of the mass which was demonstrated more by displacement of adjacent structures and small collections of gas around its periphery than by any increased density within it. The pre-operative diagnosis was a tumor of the lower pole of the left kidney with a large extrarenal component. Because of the lucency of the mass, it was considered that this represented a lipoma of the kidney. Previous experience with such cases indicated that such tumors have smooth muscle tissue as well as fat and are usually reported as myolipomata. At operation, a grapefruit-sized mass composed of fat was resected, along with the lower half of the double kidney. The tumor was encapsulated and was easily delivered. The tumor was coarsely lobulated, arose within the parenchyma of the lower pole of the kidney but most of the mass extended beyond the kidney inferiorly. In addition to the large mass, a tiny pinhead size, yellow nodule similar to the main tumor was found at a point at some distance from the main tumor on the surface of the kidney. The pathological report was a "myolipoma of the kidney."

This case is reported as an example of a group of patients, practically all of whom are females, with this type of tumor. It appears to be a hamartomatous benign new growth, primary in the kidney. In no case to date has there been evidence of metastases. For this reason, it is important to differentiate this group of tumors from fat-containing retroperitoneal tumors which often metastasize. In most instances, the finding of a myolipoma is incidental. The roentgen diagnosis is based on the fact that there is evidence of a lucent mass lesion which obscures the kidney outline and/or deforms the collecting system of the kidney.

*Case Report:* HAMARTOLIPOMA OR MYOLIPOMA OF THE KIDNEY.

#### CASE NO. 151

This was the first admission to this hospital of a 66 year old female with the chief complaint of pain in the back and legs. Back pain had been present for many years and she had been treated off and on for arthritis. Four months prior to admission, the pain radiated into both legs, the left more than the right, down to the knees. She also complained of some weakness and listlessness as well as nocturia, polyuria, frequency and occasional burning on urination. For a week prior to admission, a nonproductive cough was present. She had lost about 14 pounds within a period of six months but this was attributed to special dieting. Eleven years before admission, an operation had been performed elsewhere for right kidney stones. She had also undergone cholecystectomy and hysterectomy some time previously. Three years prior to admission, an anterior resection for a carcinoma of the sigmoid had been performed. Examination on admission showed an obese rather chronically ill-appearing female. Blood pressure was 160/84. There were rales at the base of the left chest. There were no significant neurological findings or other pertinent physical features. Hemoglobin



was 11.7 Gm. White blood count was normal. Urine showed occasional clumps of white blood cells. On one occasion, there were many red blood cells in the urine. Blood urea nitrogen was normal. Concentration of urine was normal.



Case 151, Fig. 1. Examination of the chest shows two rather discrete but poorly demarcated areas of consolidation, one in the right upper lobe and the other in the left midlung field. Each measures about  $1\frac{1}{2}$  inches in maximum diameter. In addition, there is evidence of focal atelectasis or fluid in relationship to the lesser fissure of the right lung.

Roentgen examination of the chest showed at least two discrete but rather poorly demarcated infiltrations, one on each side, measuring about  $1\frac{1}{2}$  inches in maximum diameter (Fig. 1). In addition, there was an area either of plate-like atelectasis or a small amount of fluid adjacent to the lesser fissure on the right. These findings were interpreted as most likely due to metastatic lesions. Rather diffuse osteoporotic and hypertrophic arthritic changes were noted in

the dorsolumbar spine but there was no definite evidence of a localized destructive process. Intravenous pyelography showed no gross abnormality of the

Case 151, Fig. 2. Left retrograde ureteropyelogram. The tip of the catheter was obstructed 12 cm above the ureterovesical junction. A segment of ureter about 2 inches in length immediately proximal to this was moderately dilated. In its distal portion, there was an ovoid lucent filling defect which may have been injected air since no intraluminal lesion was later found at this site. The segment of ureter intervening between this region and the pelvis of the kidney (lower arrow) is markedly narrowed and irregular in configuration. A small amount of opaque material entered the markedly dilated pelvis which presents an irregular filling defect (upper arrow) on its lateral aspect. There is also marked irregularity of the upper and lower aspects of the renal pelvis indicating similar involvement. These findings are not inconsistent with a papillary type of tumor of the pelvis of the kidney with ureteral implantation. While the gross findings at operation also suggested this diagnosis, microscopic examination demonstrated that the multiple neoplastic lesions within the pelvis and the ureter were due to metastatic mucous adenocarcinoma.



collecting system of the right kidney and no evidence of renal stones. However, there was no visualization of the left kidney. A catheter passed up the left ureter was obstructed 12 cm from the bladder. A ureteropyelogram showed a dilated segment of ureter for about  $2\frac{1}{2}$  inches proximal to the site of obstruction and

another segment of ureter immediately above this of about the same length which was markedly narrowed and irregular in configuration (Fig. 2). A small amount of opaque material entered a markedly dilated pelvis with an irregular filling defect within its center and evidence of irregularities or additional filling defects in its upper and lower portions. While the pyelographic changes were difficult to interpret, it seemed likely that there was a neoplasm of the pelvis with involvement of the ureter as well. There was, however, no clear-cut continuity between the narrowed proximal portion of the ureter and the site of obstruction.

The left kidney and upper portion of the left ureter were exposed through a lumbar incision and a uretero-nephrectomy performed. The kidney was of approximately normal size. The renal pelvis and calyces, however, were markedly dilated with numerous soft papillary excrescences protruding into the lumen. The lower pole of the kidney was infiltrated by whitish firm tissue which extended distally and around the upper portion of the ureter. The distal portion of the ureter was not exposed. On microscopy, the tumor was shown to be a metastatic mucus-producing adenocarcinoma. Postoperatively the patient did well and was discharged in 2½ weeks.

This case is another example of metastases to the ureter and renal pelvis from a sigmoid carcinoma resected three years previously. Gross metastatic lesions to the kidney and ureter are uncommon and therefore frequently not recognized. The bizarre nature of the roentgen findings in this case should have suggested the correct diagnosis.

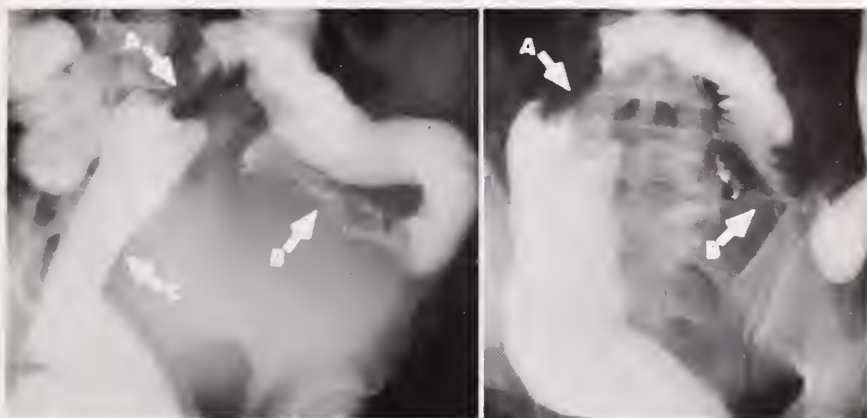
*Case Report:* METASTATIC CARCINOMA TO THE URETER AND PELVIS OF THE KIDNEY FROM A SIGMOID CARCINOMA.

#### CASE NO. 152

This was the first admission of a 43 year old white female with the chief complaint of swelling of the abdomen. This was noted originally six weeks prior to admission and was rapidly progressive. During this interval her appetite was poor and she had lost two or three pounds in weight. The last menstrual period was two or three days prior to admission. There had been no change in bowel habits but she complained of some difficulty in urination.

Examination on admission was essentially not contributory except for the the presence of a volley-ball size mass arising out of the pelvis predominantly on the left side of the abdomen. The mass appeared to be smooth and cystic and was somewhat tender on deep palpation. Hemoglobin was 11 Gm, the white blood count was not remarkable. The urine showed a few red and white cells. Barium enema examination confirmed the presence of a large homogeneous soft tissue mass on the left side of the pelvis which indented the left anterior aspect of the rectosigmoid in rather smooth fashion (Fig. 1). There were, however, multiple scalloped indentations on the distal sigmoid which indicated that the mass was not a single simple cyst. Moreover, in the distal sigmoid there was a markedly constricting lesion (about 1½ inch in length) which had the typical appearance of an intrinsic carcinoma of the colon. Because of this latter

finding, the differential diagnosis roentgenologically was not unequivocal. The possibility of a primary carcinoma of the sigmoid with huge extrinsic extension could not be entirely excluded. Because the narrowed segment of the sigmoid was concentrically located and showed typical overhanging edges with ulcerated mucosa in the narrowed central channel, the possibility that the sigmoid changes were due to infiltration by a carcinoma of the ovary was not seriously considered. The third possibility of an independent primary carcinoma of the colon and an independent lesion of the ovary could not be excluded.



Case 152, Fig. 1A. In the oblique projection, the lesion in the sigmoid (arrow A) is somewhat better demonstrated. The extrinsic defect on the sigmoid (arrow B) shows multiple areas of scalloping rather than a single arcuate contour. In this projection, a smooth indentation due to extrinsic pressure (arrow C) is also evident on the anterior and left aspect of the rectosigmoid. Occupying the entire area below the sigmoid, here is a homogeneous soft tissue density.

Case 152, Fig. 1B. Barium enema examination shows a constricted segment about  $1\frac{1}{2}$  inch in length in the distal sigmoid (arrow A) with a typical overhanging edge. In addition, there is an extrinsic scalloped indentation (arrow B) on the under aspect of the proximal sigmoid.

Three days after barium enema examination, because of rapidly progressive distension, a trochar was inserted in the left lower quadrant and about two quarts of dark tea-colored fluid was removed. On gram stain, no bacteria were demonstrated. The sediment of the fluid showed numerous polymorphonuclear leucocytes, red cells and some mesothelial cells but no tumor cells were recognized.

The patient was explored through a lower abdominal incision. The left ovary was found to be occupied by a tumor almost a foot in diameter. Separate from this tumor, there was also a typical carcinoma of the sigmoid. The serosal aspect over the sigmoid tumor was puckered and there were many firm lymph nodes. In addition to resection of the sigmoid, a cecostomy, a bilateral salpingo-oophorectomy, and a hysterectomy were performed. Pathological examination showed that the sigmoid carcinoma was ulcerating and fungating. The mass in



the left ovary was the size of a grapefruit and weighed 920 Gm. It did not have the appearance at the time of removal of a cyst. On section, it was soft, pliable, and pinkish in color with multiple yellowish foci. Microscopic examination showed that the ovarian tumor was a massive metastatic adenocarcinoma. Postoperatively, the patient did quite well and the cecostomy was closed without incident.

*Case Report:* PRIMARY CARCINOMA OF THE SIGMOID WITH HUGE OVARIAN METASTASIS SIMULATING OVARIAN CYST.

#### CASE NO. 153

This was the first admission of a 58 year old white male with the chief complaints of increased sweating, unilateral exophthalmos, and a rapid pulse. Ten days prior to admission, the patient consulted his physician because of protrusion of the left eyeball. His physician discovered the presence of glycosuria as well as tachycardia. Insulin was started and further investigation suggested because of the possibility of hyperthyroidism. He was admitted to the hospital for this purpose. Examination on admission showed an obese male in no distress. Blood pressure was 188/110. He had a moderate proptosis on the left side with a mild midlag. There was no palpable evidence of any tumor mass adjacent to the eyeball. A large lymph node was found in front of the left ear. This was about one centimeter in diameter, quite firm, and not tender. Below the angle of the jaw, there was also a mass approximately 3 cm in diameter, hard, and only slightly movable. The patient subsequently stated that the appearance of proptosis of the left eye had been associated with left supraorbital pain of dull, aching character. At no time, however, did he complain of double vision or impairment of vision. The urine, on admission, showed sugar and acetone, both of which disappeared shortly after insulin administration. Sedimentation rate was 76 mm per hour, hemoglobin 13.2 Gm, white blood count 5,850 with 62 per cent segmented polyps, 17 per cent band polys with slight toxic granulation. Iodine-131 uptake studies and protein-bound iodine blood concentrations were within normal limits. Prior to these studies, however, roentgen examination of the skull had been performed and was quite revealing (Figs. 1A, 1B, 1C). There was marked clouding of all of the sinuses as well as of the nasal cavities. The bony margin, particularly of the left frontal sinus, was markedly irregular and a portion of the floor of the frontal sinus, that is, the roof of the orbit, was depressed inferiorly with irregular sclerotic new bone formation. This new bone formation extended into the zygomatic process of the frontal bone, lateral to the frontal sinus. The lamina papyracea in the medial wall of the orbit on the left side was not seen as well as on the right. Various interpretations of the roentgen findings were given by different observers. It was evident that there was expansion of the left frontal sinus with destructive, presumably osteomyelitic changes in the wall of the sinus. Peripheral bone formation indicated that this process was of long standing. In the presence of an obvious bilateral diffuse sinusitis, it was felt that the most likely diagnosis was obstruction to



Case 153, Fig. 1A. Postero-anterior examination of the skull shows diffuse clouding of the ethmoid sinuses. The lamina papyracea on the left (medial arrow) is indistinct. The bony wall of the left frontal sinus including the orbital margin is hazy with sclerotic changes laterally and inferiorly. New bone formation results in a thick, irregular ledge of bone (lateral arrow) protruding downwards into the orbital cavity.



Case 153, Fig. 1B. View of the skull in the Water's position confirms the absence of the lateral wall of the ethmoid sinus on the left side posteriorly (arrow). The irregular, mottled, lucent and partially sclerotic roof of the orbit on the left side is also evident. Both antra are markedly cloudy. The nasal cavities are filled with soft tissue.

the opening of the left frontal sinus with secondary infection and pseudomucocele formation.

A variety of clinical diagnoses were also entertained during the course of this patient prior to operation. Originally, the possibility of hyperthyroidism seemed most likely. When an organic basis for unilateral exophthalmos was found, the possibility of a sphenoidal ridge meningioma was considered. Left carotid angiogram (not illustrated) was performed and showed no evidence of an intracranial mass or aneurysm. Several days after admission, there was a suggestion



Case 153, Fig. 1C. In the lateral projection, the new bony ledge (arrow) is thick and extends well posteriorly as well as inferiorly. It is likely that a supraorbital ethmoidal cell, originally present, is confluent with the frontal sinus as a result of bone destruction. The sphenoid sinus is diffusely cloudy.

of a soft tissue mass within the medial portion of the orbit displacing the globe of the eyeball downward and laterally. There was no bony tenderness. The mass within the orbit became obvious in the next several days and marked congestion of the bulbar conjunctiva with tearing appeared.

Ten days after admission, exploration of the left frontal sinus area was done. A large amount of infected mucoid material was found in the frontal sinus with obvious destruction of the wall of the sinus. Polyps and granulation tissue were found filling the sphenoid and ethmoid sinuses and the nasal cavity. The surgeon felt, however, that some of the tissue in the region of the posterior ethmoids was unusually firm and solid. A portion of this tissue was sent for frozen section and was reported as anaplastic carcinoma. This was confirmed

subsequently by paraffin sections which showed "fragments of partially necrotic anaplastic carcinoma as well as bone fragments partially infiltrated by carcinoma." Postoperatively, the patient was given high voltage x-ray therapy.

This patient is of considerable interest from both the clinical and roentgen points of view. Despite the obstruction to the frontal sinus with abscess formation and infection as well as infiltrating tumor, the patient's history went back no further than two weeks. The correct diagnosis of an anaplastic carcinoma arising in the posterior ethmoids was not suspected until operative intervention and, even at that time, could easily have been overlooked.

*Case Report:* ANAPLASTIC CARCINOMA OF THE ETHMOID SINUS WITH CHRONIC ABSCESS OF THE FRONTAL SINUS.

#### ACKNOWLEDGMENTS

This case is presented through the courtesy of Dr. Sidney Gross and Dr. Max Som.

#### CASE NO. 154

This was the first admission to this hospital of a 61 year old male with the chief complaint of pain in his right leg for about two years. Five years previously, the patient had undergone an extrapleural pneumonectomy elsewhere for an invasive bronchial adenoma of the right upper lobe bronchus discovered because of hemoptysis. At that time, the mass contained areas of calcification and ossification ranging from 0.3 to 4 cm in diameter. Lymph nodes removed

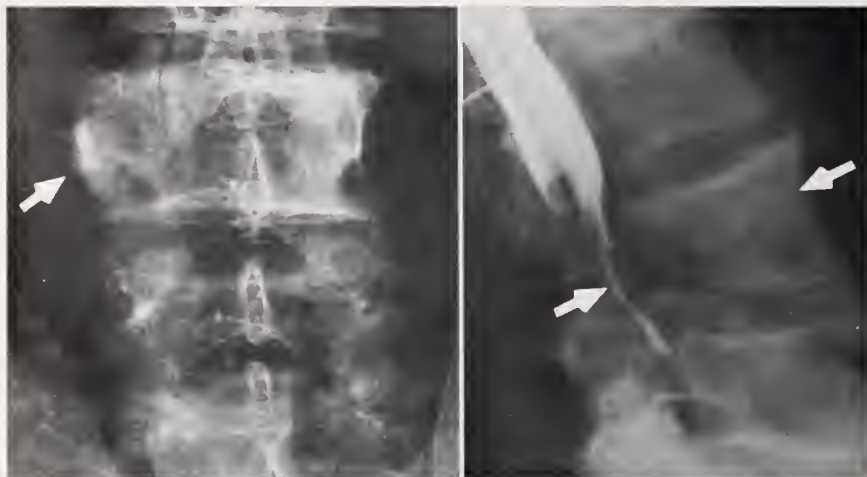


Case 154, Fig. 1A. In the lateral view, marked bulging of the ribs by the mass (arrows) is seen. The bone in the tumor has a trabeculated appearance.

Case 154, Fig. 1B. The mass involving the left thoracic wall extends into the pleural cavity and into the soft tissues of the chest. It is well delineated and sharply demarcated. Throughout its extent, there are innumerable strands of new bone formation.



from the region of the carina showed only reactive changes. Four years after the pneumonectomy, the patient was readmitted to the original hospital because of pain in the lower back radiating to his right leg as well as pain in the left chest with the appearance of a mass in this latter region. A needle aspiration of this mass in the wall of the left chest was performed and the tumor tissue was reported as invasive bronchial adenoma similar to the tumor of



Case 154, Fig. 2. The antero-posterior projection of the lumbar spine shows new bone formation of a trabecular character (arrow) extending into the soft tissues from the lateral aspect of the body of the 4th lumbar vertebra. The adjacent pedicle is destroyed. (The midline opaque sutures were the result of a subtotal gastrectomy for duodenal ulcer performed 12 years previously.)

Case 154, Fig. 3. Lateral view of the spine taken with the patient erect during the course of pantopaque myelography shows almost complete block to the caudal flow of the opaque material at the level of the 4th lumbar vertebra. The small trickle of pantopaque which passed this site (posterior arrow) is deviated posteriorly. The posterior aspect of the 4th vertebral body shows irregular lucent areas of destruction. The upper portion of this vertebra (anterior arrow) is relatively sclerotic.

the lung removed four years previously. The patient was admitted to this hospital because of persistent right leg pain which had become almost constant.

Examination on admission showed a well-developed, well-nourished male in no acute distress. In the left axilla, attached to the chest wall, there was a mass about two inches in diameter. The right knee jerk was absent. The left knee jerk was diminished. He walked with a slight limp of the right leg. The neurological consultant felt that the patient had a radiculopathy involving the L3, L4 and L5 lumbar nerves particularly on the right side. Hemoglobin was 10.9 Gm, and the white blood count 6,800. Urine showed 1 to 3+ albumin with a specific gravity of 1032. At times, the urine contained many white blood cells.

Roentgen examination of the mass (Figs. 1A, 1B) in the chest wall showed this to be about two inches in diameter and rather globular in configuration projecting both into the pleural cavity and into the soft tissues of the chest wall. Throughout this mass, there were innumerable radiating strands of bone. Examination of the lumbar spine (Fig. 2) showed trabeculated new bone arising from the lateral aspect of the body of the 4th lumbar vertebra and irregular destruction of the posterior aspect of this vertebra (Fig. 3). In the region of the anterior superior iliac spine on the right side (Fig. 4), the bone was also



Case 154, Fig. 4. The wing of the right ilium extending into the anterior superior iliac spine (arrows) is broadened as a result of trabeculated new bone formation.

expanded with increased trabecular densities. Pantopaque myelography (Fig. 3) showed evidence of a block due to an extradural tumor at the level of the interspace between L3 and L4. Laminectomy was performed at this site with decompression and partial removal of metastatic tumor. The bone was very soft and vascular and the tumor mass extended into the muscles adjacent to the spine. The postoperative course was quite stormy and the patient ceased 12 days after the operation. No autopsy was obtained.

It is now well known that a bronchial adenoma may become invasive and metastasize to distal organs particularly bones and that these metastatic lesions may be sclerotic, presumably on a reactive basis. In this case, new bone forma-

tion occurred in large amounts in the original tumor and in the metastatic lesions extending into the soft tissues. In other words, bone formation appeared to be the result of tumor growth rather than irritation.

*Case Report:* INVASIVE BRONCHIAL ADENOMA WITH EXTENSIVE NEW BONE FORMATION WITHIN THE ORIGINAL TUMOR AND METASTATIC DEPOSITS.

#### ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Irving Sarot.

#### CASE NO. 155

PRESENTED BY CLAUDE BLOCH, M.D., AND MAURICE WOLF, M.D.

This 71 year old female underwent total cystectomy and a bilateral uretero-ileostomy in March 1960 for a large infiltrating and ulcerating transitional



Case 155, Fig. 1A. Antero-posterior view of the right knee shows sharply localized destruction of the fibula below the head. The continuity of the bone is maintained by amorphous periosteal new bone formation (arrow A) which extends distally around the shaft (arrow B). Irregular bone or calcium deposits extend into the soft tissues medially (arrow C).

Case 155, Fig. 1B. In the lateral projection, the eccentric character of the defect (arrow) is not evident. There is no discrete soft tissue mass but the soft tissue adjacent to the defect has a homogeneous dense appearance.

cell carcinoma of the bladder neck. The patient had an uneventful recovery and did well until four months later when she noted the onset of painful swelling, local tenderness, and skin discoloration of the right knee and leg. The patient also complained of intermittent vague lower abdominal pain.

Physical examination was noncontributory except for a right leg diffusely swollen from the knee to just above the ankle. This was most marked on the lateral aspect of the leg. The edges of the swelling were poorly demarcated. The skin had a slight bluish discoloration and there was some brawny edema of the upper two-thirds of the leg.

Roentgen examination of the right knee joint and leg revealed a five centimeter long elliptical destructive lesion involving the medial and posterior aspect of the fibula immediately distal to the head of the fibula. In the frontal projection (Fig. 1A), the edge of the lytic defect was smoothly demarcated and rounded, whereas in the lateral view, its anterior border was irregular and less well defined. There was periosteal new bone formation along the edges of this destructive lesion which extended distally for a distance of about four centimeters. A distinct soft tissue mass could not be delineated but the muscle mass in the upper portion of the involved leg was considerably more prominent and denser than on the other side. Films of the chest and skeletal survey of other bones were negative.

The roentgen features of the destructive lesion strongly suggested a metastatic malignant process involving the proximal fibula. A needle aspiration of the soft tissue mass in the region of the upper fibula was performed and revealed fragments of fibrous tissue showing infiltrating carcinoma, most probably of transitional cell type.

The finding of a solitary metastasis to the fibula makes this case unusual. Osseous metastases represent only approximately five per cent of metastases from carcinoma of the bladder. It is uncommon for the destructive lesion to occur distal to the knee joint.

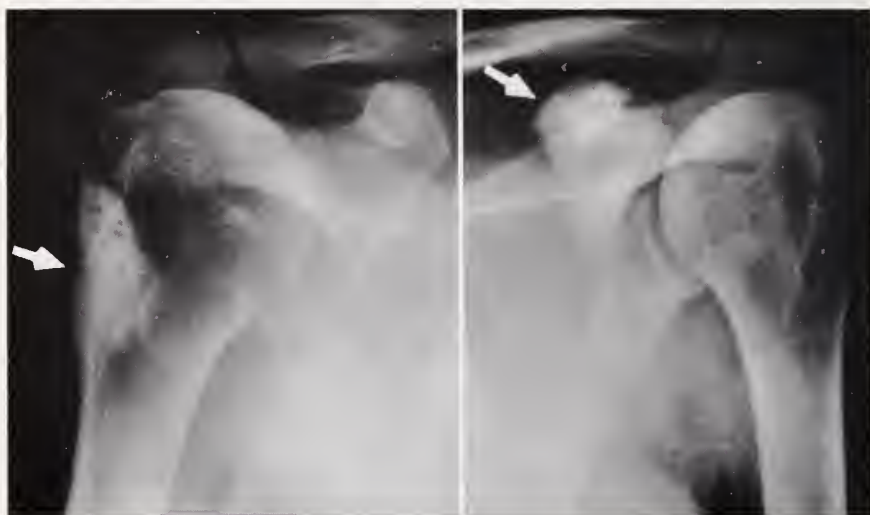
*Case Report:* TRANSITIONAL CELL CARCINOMA OF THE BLADDER; SOLITARY METASTASIS TO THE FIBULA.

#### CASE NO. 156

This was the tenth admission to this hospital of a 58 year old female with a known carcinoid syndrome. Ten years before admission, the patient began to complain of flushing of the face, episodes of depression, and frequent crying spells, symptoms initially attributed to the menopause. After an interval of three years, a chest film taken because of cough and upper respiratory infection, demonstrated infiltration in the left upper lobe with atelectasis. After bronchoscopic demonstration of a polypoid lesion in the left upper lobe bronchus reported as a carcinoma of the lung, a left pneumonectomy was performed. Subsequent review of the slides, however, showed it to be a typical carcinoid. At the time of the pneumonectomy, adjacent lymph nodes were also involved. The patient did well for a period of about five years after which she began to notice recurrent paroxysmal brick red flushing and explosive watery diarrhea, short-



ness of breath on exertion, fatigability and episodes of paroxysmal nocturnal dyspnea. She lost 20 or 25 pounds. During the course of the various admissions, a grade III harsh systolic murmur over the pulmonic area and right ventricular hypertrophy appeared. A diagnosis of pulmonic stenosis was made. The liver was firm, diffusely nodular and enlarged 5 to 6 fingerbreadths below the costal margin. Liver biopsy demonstrated metastatic involvement from bronchial "adenoma" of the lung. Of interest was the fact that, on the current admission,



Case 156, Fig. 1. In the lateral aspect of the right humerus, there is a well-demarcated, wedge-shaped area of sclerotic bone (arrow). Trabecular structure, though markedly exaggerated, is partially retained. The destructive or metastatic nature of the lesion is not immediately apparent.

Case 156, Fig. 2. The coracoid process (arrow) of the left scapula shows another area of sclerosis or exaggerated trabecular structure.

deep tenderness over the left shoulder was found. Roentgen examination of both shoulders was performed and showed sclerotic metastases in the right humerus (Fig. 1) and left scapula (Fig. 2). The patient was not amenable to hospital care and signed out against advice before additional investigations could be undertaken.

It is instructive to compare this case with the patient presented as Case No. 154. Similar lesions are present in both patients although in this instance, no exophytic type of growth has occurred. In the original tumor, there was no evidence of calcification or new bone formation.

*Case Report:* A CARCINOID WITH SCLEROTIC METASTASES.

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